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total haemolytic complement activity remaining in serum can be assayed by measuring the ability of serum to lyse antibody-coated red blood cells (expressed as the 50 per cent lysis point or CH50). Such techniques are useful in monitoring the activity of connective tissue diseases and vasculitis. The detection of immune complexes fixed in tissues such as the kidney can also be of diagnostic value. Complement levels in the serum may be reduced by immune complexes, although in some disorders the tendency for inflammation to raise the level of production of some complement components can make the interpretation of serum levels difficult.

Such tests should always be viewed in the clinical context and abnormalities (frequently seen, for example, in rheumatoid disease) should not in themselves be regarded as an indication for treatment.

Other more sophisticated tests of immune cell function and antibody and complement production may be valuable in rare immune deficiency disorders—either primary or secondary.

The HLA class 1 allele B27 is found in over 90 per cent of subjects with ankylosing spondylitis. Although this finding may support a clinical diagnosis, it must be remembered that the great majority of HLA-B27 positive individuals are healthy. There is no place for routine assessment of HLA-B27 status in the evaluation of suspected seronegative spondylitis.

Other investigations

Several other investigations are important in the diagnosis or monitoring of specific rheumatic diseases or their complications. Some examples are shown in Table 5.

18.4 Rheumatoid arthritis

B. P. WORDSWORTH

The term rheumatoid arthritis was first used by Sir Archibald Garrod in 1876 to describe a chronic non-suppurative inflammatory arthropathy distinct from gout and osteoarthritis. It is generally regarded as an autoimmune disease but details of its pathogenesis remain unclear. Its prevalence is remarkably consistent worldwide (approximately 1 per cent) with a few important exceptions that have helped to highlight environmental influences and the role of the immune response genes. Inflammation of the synovial joints leading to destruction of joints and periarticular tissues is the most obvious clinical and pathological characteristic of the disease, but a wide variety of extra-articular features can also develop. In contrast to gout, osteoarthritis, ankylosing spondylitis, and many other forms of bone and joint disease, there is a remarkable dirth of evidence for the antiquity of rheumatoid arthritis raising speculations that it is a relatively 'new' disease. Another remarkable characteristic of this condition is that it is confined to humans, being virtually unknown in any other species.

Aetiology

Rheumatoid arthritis has a complex multifactorial aetiology. There is considerable evidence for an important genetic component. Twin studies indicate a concordance rate of around 20 per cent in monozygotic twins, although this figure is probably influenced by the severity of the disease in the proband. Thus, concordance rates may be lower when the index twin has mild, non-erosive disease but as high as 40 per cent if only index twins with erosive, rheumatoid factor-positive disease are considered. Confirmation of an important genetic contribution comes from comparing monozygotic and dizygotic twins, since disease concordance is approximately five times higher in the former despite their presumably similar exposure to environmental influences. However, susceptibility to rheumatoid arthritis must be determined predominantly by non-genetic factors since concordance rates are substantially lower than 50 per cent.

The pan-global distribution of rheumatoid arthritis could be explained by the involvement of a ubiquitous organism. However, strong supporting evidence for this concept is lacking. Although rheumatoid arthritis has many similarities to reactive arthritis, in which a wide range of different Gram-negative organisms are known to trigger the disease, infection at sites distant from the joints has not been identified, in spite of claims that infections of the urinary tract (*Proteus* sp.) may be more common in patients with rheumatoid arthritis than in healthy controls.

Likewise, no particular organism has ever been found reproducibly in the joints of patients with rheumatoid arthritis, although there have been sporadic reports of the isolation of viruses (rubella, parvovirus), atypical mycobacteria, and mycoplasma.

Some populations appear to be at unusually high or low risk of developing rheumatoid arthritis, and the study of these has yielded some clues to its aetiology. Such observations could be explained by genetic or environmental differences. For example, the prevalence of the disease is very low in much of Africa. In the case of South African negroes there is strong support for an environmental influence: in the rural areas this ethnic group has the same low prevalence of the disease as elsewhere in rural subSaharan Africa, but this is greatly increased in those who have migrated to the townships where the prevalence is similar to that in the population of European descent. In contrast, the high prevalence (5 per cent or more) in the Yakima and Chippewa Amerindians is more likely to be, at least in part, genetically determined. Both these tribes have a high frequency (c. 70 per cent) of HLA class II alleles associated with susceptibility to rheumatoid arthritis (DR4 in the Chippewa and DR6Dw16 in the Yakima).

The genetic component of rheumatoid arthritis has been clarified by studying families, and also from the definition of specific genetic markers associated with the disease. The risk to the first-degree relatives of probands with mild, non-erosive, seronegative disease (2–3 per cent) is little greater than in the risk in the general population. In contrast, the prevalence of rheumatoid arthritis among the first-degree relatives of probands with erosive, seropositive disease may be as high as 15 per cent, underlining the importance of genetic factors in determining disease severity. Estimates of the risk to the siblings of affected individuals range between 4 and 10 per cent, but there may be a delay, of decades even, before the development of the disease in the second sibling. Increasingly, interest in the genetic component of rheumatoid arthritis has focused on immunogenetic factors, particularly the immune response genes in the major histocompatibility complex on chromosome 6.

IMMUNOPATHOLOGY

In the early stages of rheumatoid arthritis the most obvious histological changes are confined to the synovial microvasculature, which shows evidence of endothelial damage, infiltration by polymorphonuclear leucocytes, and obliteration by thrombus. In the chronic phase, polymor-

phonuclear leucocytes are less obvious but the synovium is infiltrated by large numbers of inflammatory cells (macrophages, T and B lymphocytes, dendritic cells, and plasma cells). Among the lymphocyte population, B cells appear to be somewhat under-represented while T cells with the CD4+ (helper/inducer) phenotype are increased, particularly in the perivascular areas. The plasma cells in the subsynovium synthesize large quantities of immunoglobulin, much of which is IgM and IgG rheumatoid factor (i.e. immunoglobulin with reactivity to self-IgG). The precise role of these autoantibodies in the pathogenesis of the disease is not clear, but their ability to form immune complexes that can activate complement could be important in either initiating or prolonging local inflammation within the joint. Evidence for complement activation in the inflamed joints and serositis associated with rheumatoid arthritis is demonstrated by the presence of complement breakdown products such as C3a and C5a, both highly potent chemotactic agents for polymorphonuclear leucocytes and powerful mediators of inflammation. Rheumatoid factors are not specific for rheumatoid arthritis, being found in some 5 per cent of the normal population (usually in low titre) and in other diseases, particularly chronic infections such as tuberculosis, leprosy, and osteomyelitis. Their presence may precede the development of rheumatoid arthritis by months or even years, while in a minority of cases classical IgM rheumatoid factor may be persistently absent or only detectable long after the development of the disease.

Several observations suggest that the inflammatory reaction in rheumatoid arthritis is a T-cell mediated phenomenon. First, there is a clear physical association between CD4-positive T cells and dedicated antigen-presenting cells (dendritic cells and cells of the macrophage/monocyte lineage) in the perivascular areas of the synovium. Second, certain therapeutic measures including thoracic duct drainage, total body lymphoid irradiation, and, perhaps, the use of anti-CD4 monoclonal antibodies are associated with a decline in circulating T-cell numbers as well as clinical improvement. Third, cyclosporin, which is primarily

directed against CD4-positive T cells is effective in rheumatoid arthritis. Finally, a role for a selected population of T cells might be inferred from the limited array of HLA class II antigens (eg. DR4, DR1) that are strongly with associated with rheumatoid arthritis. Most of these cells are activated and have a mature (CD45Ro) phenotype but, somewhat surprisingly, it has been difficult to demonstrate increases in the levels of cytokines (interleukin-2, interleukin-4, and γ-interferon) that might have been expected in the synovium and synovial fluid. One explanation for these findings might be that there is an accumulation of an unusual lymphocyte subset in the synovium. In contrast, large quantities of macrophage-derived cytokines (interleukin-1, tumour necrosis factor-α) are present, perhaps indicating an important role for the macrophage in the synovial inflammation. Preliminary trials of the efficacy of chimeric antitumour necrosis factor antibodies have proved promising.

Unusual glycosylation patterns of immunoglobulins have been observed in patients with rheumatoid arthritis, similar to those which may be seen in mycobacterial infections and sarcoidosis. Curiously, these changes in glycosylation have also been noted in the unaffected spouses of those with the disease. It has been suggested that this may render self-immunoglobulins potentially immunogenic, leading to the development of rheumatoid factors, but this is speculative. A reduced capacity to oxidize certain sulphur-containing compounds has also been described in patients with rheumatoid arthritis. Whether either of these phenomena is of primary importance is not known, but both have been used successfully as predictors of progression to chronic rheumatoid arthritis in patients with signs of early inflammatory joint disease.

IMMUNOGENETICS

Susceptibility to rheumatoid arthritis is associated with the immune response (HLA) genes in the major histocompatibility complex. The products of these genes are cell-surface glycoproteins that play a fun-

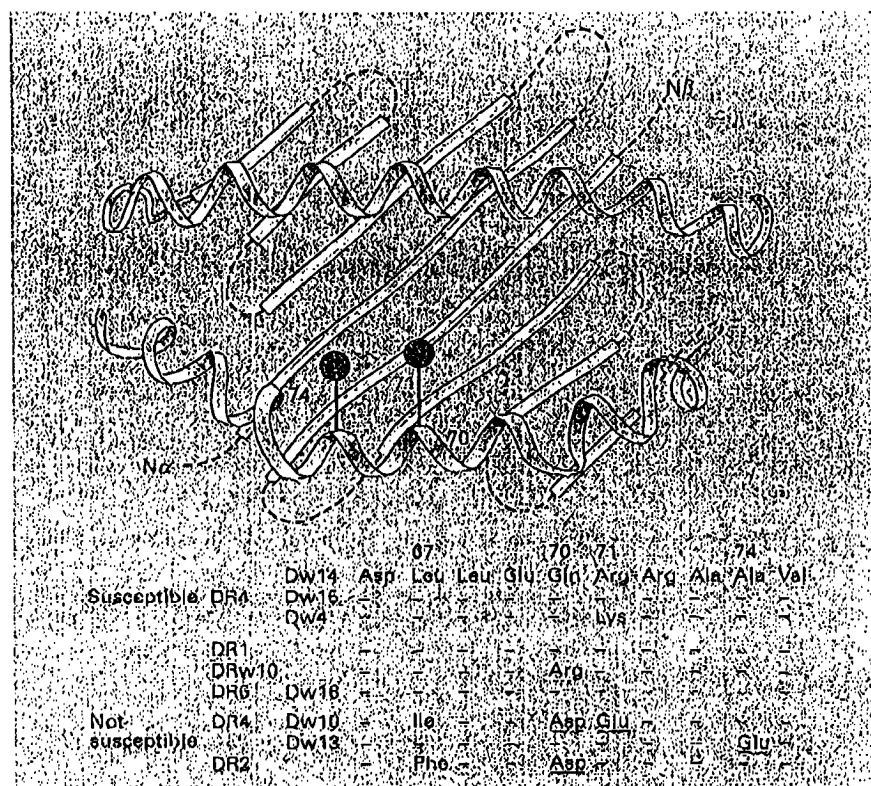|			67	70	71	74
Susceptible DR4	Dw14	Asp	Leu	Leu	Glu	Gln	Arg	Arg	Ala	Ala	Val
	Dw15						Arg			
	Dw4						Lys			
	DR1						Arg			
	DRw10						Arg			
	DR6	Dw16								
Not susceptible	DR4	Dw10	Ile		Asp Glu				
		Dw13						Glu		
	DR2			Phe			Asp			

Fig. 1 Schematic representation of some HLA-DR molecules positively or negatively associated with rheumatoid arthritis. Charged amino-acid substitutions (underlined) at positions 71 and 74 in the antigen binding-site are crucial in influencing susceptibility among the DR4 subtypes.

damental role in the binding of peptide antigens and their presentation for recognition by T cells. The class I antigens (HLA-A, -B, and -C) are present on all nucleated cells and are particularly important in the immune surveillance of viral infections. The class II antigens (HLA-, DR, -DQ, and -DP), in contrast, are found only on certain cells specialized in antigen presentation, such as dendritic cells, macrophages, and also B lymphocytes.

The observation from family studies that affected sibling pairs tend to inherit HLA haplotypes in common from their parents more frequently than would be expected by chance incriminates a gene (or genes) linked to HLA in susceptibility to rheumatoid arthritis. Furthermore, in most populations there are strong associations with specific alleles at the HLA-DRB1 locus which encodes the DRβ chain. Thus, the relative risk associated with alleles at this locus, defined serologically, ranges from nearly twofold for DR1 to over six-fold for DR4. The most likely explanation for this lies in the structure of the HLA molecule, in which polymorphic amino acid residues are concentrated around the antigen-binding site (Fig. 1). Those molecules which are associated with the disease share considerable homology in this region which is likely to have considerable influence on the range of peptide antigens that can be bound by particular HLA molecules. This is most clearly exemplified by the differential association of the various allelic subtypes of DR4 with rheumatoid arthritis where even one amino acid substitution in this region is sufficient to abrogate susceptibility to the disease (Table 1).

The association between DR4 and rheumatoid arthritis is strongest in the more severe variants of the disease. In community-based studies, which tend to include many milder cases, the association may be weak or even absent; in patients with erosive, seropositive disease 70 per cent of patients are likely to be DR4 positive, compared to about 25 per cent of the normal Caucasian population; in the Felty syndrome the frequency of DR4 is over 90 per cent. Furthermore, in the more severe forms of rheumatoid arthritis there is an increased frequency of the Dw4 subtype of DR4 (up to 90 per cent in the Felty syndrome) and also of DR4 homozygotes, the majority of whom have the Dw4/Dw14 genotype. It is likely that HLA accounts for no more than 30 per cent of the total genetic effect in rheumatoid arthritis, although no other genes contributing to susceptibility have yet been defined.

Clinical features

Rheumatoid arthritis is a systemic disorder characterized by a chronic inflammatory synovitis which typically affects the peripheral joints but may affect any synovial joint in the body. In addition to the articular features that are the hallmark of the disease, many other tissues may also be affected, although this, like the severity of the articular disease, is highly variable. It is a disease of exacerbations and remissions, the clinical variability of which suggests that it might represent the end result of a number of different disease pathways. Diagnosis is based on the aggregation of a series of common clinical features rather than any specific pathognomonic abnormality; until there is a fuller understanding of the aetiology of the disease the possibility that the single diagnosis 'rheumatoid arthritis' masks considerable heterogeneity cannot be excluded.

The development of various classification systems, based predominantly on clinical criteria, has been of substantial benefit in the study of the epidemiology and aetiology of the disease. The diagnostic criteria developed by the American Rheumatism Association in 1958 have been used widely. They allow the recognition of three grades of rheumatoid arthritis according to the number of diagnostic criteria present ('classical', seven or more criteria out of 11; 'definite', five criteria, 'probable', three criteria). However, the specificity of these criteria for rheumatoid arthritis is considerably increased if the milder variants are excluded. For this reason the 1987 American College of Rheumatology criteria, corresponding approximately to the 1958 'classical' and 'definite' groups, are now generally employed (Table 2). In individuals presenting with early inflammation of the joints, these criteria have proved good

predictors of those likely to progress to chronic destructive rheumatoid arthritis.

DISEASE PREVALENCE AND ONSET

Rheumatoid arthritis may occur at any age but has a peak incidence in the fifth decade. The lifetime incidence of the disease in women (1.8 per cent) is three times that in males (0.5 per cent) and the prevalence of the disease in women over 65 years old is more than 5 per cent. The sex difference is most pronounced (as high as 6:1) in those with early onset disease but is almost equal by the age of 65. The disease starts twice as commonly in winter, but whether this represents a non-specific effect, such as the increased sensitivity to joint symptoms, or a more specific process, such as the precipitation of vasculitis, is not clear. Several distinct patterns of onset are recognized which can be of some use in predicting the prognosis.

Palindromic onset

In about one-fifth of patients with rheumatoid arthritis, persistent joint disease may be antedated by repeated attacks of acute self-limiting synovitis, affecting a variable number of joints. Typically the inflammation develops over a few hours and is accompanied by erythema and swelling of the affected joints but resolves completely within 48 to 72 h, leaving no residual features. About 50 per cent of individuals who suffer from attacks of palindromic rheumatism ultimately develop chronic rheumatoid arthritis, and they can usually be identified by the presence of rheumatoid factor in the blood, although this may not be present at the outset. The number of joints involved is usually small but increases with time and with the onset of persistent joint disease. If joint symptoms are sufficiently frequent to be troublesome during the palindromic phase, they can often be controlled by intramuscular gold injections or D-penicillamine (often in low doses) as in the case of established rheumatoid arthritis.

Explosive onset

In about 10 per cent of cases the onset of the disease is very rapid, even overnight, with severe symmetrical polyarticular involvement. Many patients with this type of onset do surprisingly well in the long term.

Systemic onset

This is particularly common in middle-aged men in whom non-articular features may dominate the clinical picture. Fever, myalgia, weight loss, anaemia, pleural effusions, and vasculitic lesions may be severe, sometimes in the absence of marked joint pathology. Although rheumatoid factor is usually present in high titres, it is often be necessary to exclude other causes such as other connective tissue disorder, malignancy, or infection.

Insidious onset

The majority of cases of rheumatoid arthritis develop insidiously over weeks or months, with gradually increasing joint involvement. This pattern of onset, which is seen in up to 70 per cent of cases, is associated with a relatively poor prognosis. Progression from predominantly peripheral small-joint disease to the involvement of the more proximal joints, including the knees and hips, is the most common pattern. However, in a subset of patients the earliest joint involvement is in the knees and wrists, those patients are particularly likely to be positive for IgA rheumatoid factor.

Polymyalgic onset

Limb girdle muscle symptoms may precede the onset of an overt arthropathy, particularly in the elderly. Not all patients with this pattern are rheumatoid-factor positive and it may be difficult to distinguish with certainty from polymyalgia rheumatica. It is therefore of considerable

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Table 1 *Differential association of rheumatoid arthritis with the various subtypes of HLA-DR4 in the United Kingdom. HLA-Dw4 and Dw14 are positively associated while Dw10 and Dw13 are negatively associated*

	n	Dw4	Dw14	Dw10	Dw13
DR4-positive controls	185	119 (64%)	53 (29%)	7 (4%)	15 (8%)
DR4 positive rheumatoid arthritis	178	133 (74%)	66 (37%)	0	2 (1%)
Probability		0.02	0.05	<0.01	0.01

Table 2 *American College of Rheumatology criteria for rheumatoid arthritis*

1. Morning stiffness of at least 1 h
2. Arthritis of three or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor positive
7. Typical radiographic changes in the hand and wrist

Criteria 1–4 must have been for at least 6 weeks.

interest that both these conditions are associated with the HLA-DR4 antigen. The initial response to corticosteroid therapy in these cases is impressive but is less well maintained as progressive synovitis supervenes.

Mono- and pauci-articular onset

In young women there may initially be very limited joint involvement, particularly involving the knees. While there is no doubt that a proportion of these cases go on to develop full-blown rheumatoid arthritis, many do not. It is therefore important to exclude other potential causes of monoarthritis, such as low-grade infection or pigmented villonodular synovitis. Intermittent hydrarthrosis causes effusions which recur with remarkably consistent periodicity in the absence of pronounced systemic or joint inflammation. The sedimentation rate and C-reactive protein are normal and joint fluid white cell counts are typically less than 200/mm^3. Patients with such limited joint disease who are persistently seronegative for rheumatoid factor usually pursue a benign course and probably represent an entirely different type of joint disease from classical rheumatoid arthritis.

JOINT FEATURES

Rheumatoid arthritis is typically a distal, symmetrical, small-joint polyarthritis involving the proximal interphalangeal and metacarpophalangeal joints of the hands, the wrists, metatarsophalangeal joints, ankles, knees, and cervical spine. The shoulders, elbows, and hips are less frequently involved, but can be a major source of morbidity. Any synovial joint in the body may be affected, including the cricoarytenoid and the temporomandibular joints. In addition, periarticular synovial structures, such as bursae and tendon sheaths, are commonly inflamed.

It may be difficult to distinguish between symptoms and signs of joint disease due to inflammation and those that result from secondary mechanical problems arising from joint destruction. This is an important distinction since it will often dictate the most appropriate form of treatment. Anti-inflammatory and disease-modifying drugs may be appropriate in the early inflammatory phase, but the use of analgesics and physical approaches, such as splints or corrective surgery, would be more likely to aid patients with severe joint damage.

The most common symptoms described by patients are pain and pronounced stiffness. The latter frequently exhibits a diurnal rhythm, worse on rising in the morning and then recurring towards the evening, perhaps reflecting the diurnal variation in plasma cortisol levels. Gentle activity may alleviate the symptoms but is followed by stiffening or 'gelling' with subsequent inactivity. The affected joints are frequently tender, swollen, and warm and there may be limitation of both active and passive movement. Muscle wasting serves to accentuate the local swelling of the joint, which is in part due to proliferation of the synovial tissue and in part to synovial effusion within the joint. Progressive destruction of the articular cartilage, subchondral bone, and periarticular soft tissues eventually combine to produce the characteristic deformities seen in long-standing rheumatoid arthritis.

In parallel with these clinical changes there are characteristic radiological appearances which may be helpful in the diagnosis of early rheumatoid arthritis and in monitoring its progress (Fig. 2). In the early stages of the disease it is common for the first evidence of erosions to be in the feet, and these should always be included in diagnostic views. Radiological changes include:

(1) soft-tissue swelling;
(2) juxta-articular osteoporosis;
(3) loss of joint space due to erosion of the articular cartilage;
(4) bone erosions at the points of attachment of the synovium; and
(5) joint deformities.

Fig. 2 Typical radiological features of rheumatoid arthritis in the metacarpophalangeal joints, showing osteoporosis, joint space narrowing, periarticular erosions, and angular deformity.

UPPER LIMBS

Hands and wrists

The appearance of the hands in rheumatoid arthritis is highly characteristic. However, there are numerous potential patterns of deformity, and distinction from other arthropathies is occasionally difficult. Early in the disease there may be soft-tissue swelling around the affected joints. Involvement of the proximal interphalangeal joints gives a spindle-shaped appearance to the fingers, and soft-tissue swelling can be observed over the ulnar styloid, and in the second and third metacarpophalangeal joints. Distal interphalangeal joint involvement is less common (about 15 per cent of cases) but rheumatoid arthritis may sometimes be superimposed on pre-existing osteoarthritis of these joints.

Tenosynovitis of the long flexor tendons in the palm of the hand may exacerbate stiffness of the fingers and cause 'trigger finger'. This may be associated with palpable crepitus over the tendon on active or passive movement of the corresponding finger. Similar synovitis at the wrist within the flexor retinaculum may cause compression of the median nerve with the typical features of carpal tunnel syndrome—paraesthesiae of the first three digits and the radial side of the ring finger, wasting and weakness of the thenar muscles, with night pain frequently extending proximally as far as the elbow; typically these symptoms can be relieved by shaking the hand or movement of the fingers. Tinel's sign is sometimes positive but relatively insensitive. Phalen's sign (pressure over the carpal tunnel with the wrist in flexion) may be more useful, not only because it is more frequently positive but also because it reproduces the symptoms accurately. The diagnosis can be confirmed if necessary by nerve conduction studies.

On the dorsal surface of the wrist, synovitis of the extensor tendons is common and may lead to rupture (Fig. 3). A 'dropped finger' affecting the little finger is an important indication for surgical exploration and synovectomy, since it may presage the progressive rupture of the rest of the extensor communis tendon. Similar rupture of the extensor pollicis longus and extensor indicis proprius may occur.

Persistent synovitis with erosion of the articular surfaces, weakening of the joint capsules, and muscle weakness, with or without tendon rupture, will inevitably lead to deformities. There are several commonly occurring variants:

Fig. 3 'Bull's horn' deformity due to rupture of the extensor communis tendon from synovitis near the ulnar styloid. Selective sparing of the extensor indicis proprius and extensor digiti minimi tendons has in this instance preserved the ability to point the index and little fingers independently.
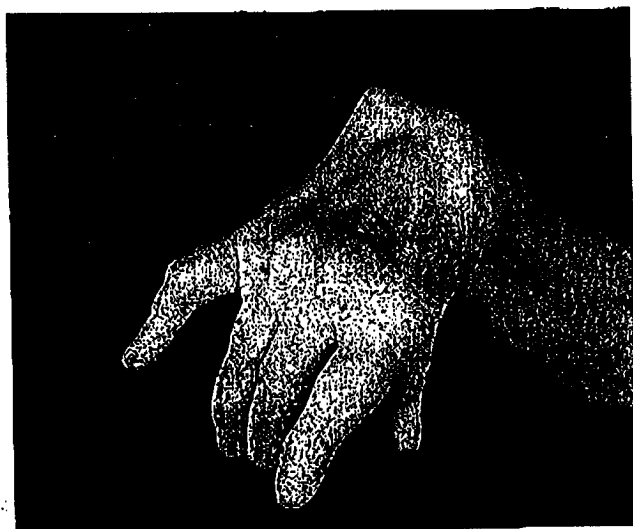
Volar subluxation of the fingers at the metacarpophalangeal joints occurs as a result of destruction of the articular cartilage, and subsequent instability of these joints. Since the flexor tendons provide the strongest force acting across these joints progressive subluxation towards the palm may develop, leaving the metacarpal heads relatively prominent.

Ulnar deviation and subluxation of the fingers as a result of instability of the metacarpophalangeal joints. The fingers may tend to drift in an ulnar direction because of the ulnar vector of the action of both the flexor and extensor finger tendons. The process may be exacerbated by radial deviation of the carpus and also by ulnar subluxation of the extensor tendons if the supports which usually hold them in place over the centre of the metacarpophalangeal joints are weakened by synovitis (Fig. 4).

Swan neck deformities occur following volar subluxation of the proximal phalanges at the metacarpophalangeal joints, with subsequent contracture of the intrinsic muscles which become extensors rather than flexors of the proximal interphalangeal joints. Compensatory flexion of the distal interphalangeal joint occurs as a result of a tenodesis effect as the flexor digitorum profundus tendon is stretched over the hyperextended proximal interphalangeal joint.

Boutonnière (button-hole) deformity occurs when a chronic effusion within the proximal interphalangeal joint stretches or even ruptures the dorsal slip of the extensor hood, allowing dorsal migration of the joint through the discontinuity. A similar process at the carpometacarpal joint of the thumb may give rise to the Z-thumb deformity.

Piano-key sign can be detected when weakening of the distal radioulnar ligament by synovitis allows the distal ulna to migrate dorsally so that it overrides the radius (caput ulnae syndrome). The ulna can be depressed by pressure like a piano key (while the patient emits a note!). Progressive destruction of the carpal joints may be followed by volar subluxation and ultimately ankylosis.

Carpal collapse and fusion may occur late in the disease, particularly in those with an early onset rheumatoid arthritis, when instability of the wrist may lead to collapse of the carpal bones, causing foreshortening of the carpus and, ultimately, spontaneous fusion of the wrist.

Elbows and shoulders

Involvement of the elbows is less common than of the wrist but severe destruction may occur, leading to pronounced deformity and disability.

Fig. 4 Volar and ulnar subluxation of the fingers at metacarpophalangeal joints which results respectively from the relative strength of the long flexors and the ulnar direction of pull arising from both the long flexors and extensors. Cutaneous nodules are present on the fingers.
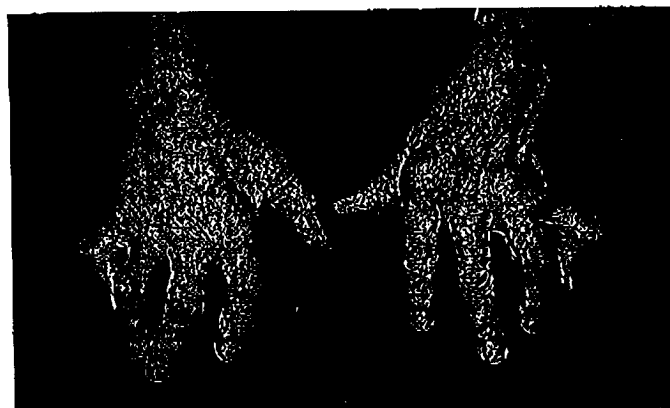
The radiohumeral joint is more commonly symptomatic than the humer-oulnar joint and presents problems particularly with pronation/supination. Periarticular structures (olecranon bursa, ulnar nerve) may also be affected by synovitis and subcutaneous nodules are commonly found on the extensor surface of the forearm close to the elbow.

Pain around the shoulder may arise from the glenohumeral joint itself, periarticular structures (particularly the subacromial bursa), the acromioclavicular joint, or the cervical spine. Frequently more than one cause may coexist, necessitating careful evaluation of the anatomical cause of the pain if appropriate treatment is to be applied. There may be inflammation of the subacromial bursa or supraspinatus tendon in addition to glenohumeral joint synovitis, producing a typical painful arc syndrome. Involvement of the acromioclavicular joint can give rise to pain particularly with overhead activities, and is associated with localized tenderness. Referred pain from the neck or cervical radiculopathy may closely mimic shoulder pathology but tends to persist at rest. In late disease of older people, severe destruction of the shoulders can occur, with loss of the whole of the head of the humerus.

LOWER LIMBS

Feet and ankles

Involvement of the feet is common from an early stage of the disease. It frequently gives rise to problems which go unrecognized despite the fact that they can often be overcome relatively simply by the provision of appropriate footwear. Active synovitis of the metatarsophalangeal joints, with or without effusions, leads to spreading of the forefoot and a marked increase in width, necessitating a larger shoe fitting. Collapse of the transverse arch of the forefoot causes the weight to be taken predominantly on the second and third metatarsal heads rather than the first and fifth which is customary (Fig. 5). Patients frequently complain of pain arising in the ball of the foot (metatarsalgia) which can vary in intensity from 'walking on pebbles' to 'like walking on broken glass'. Dorsal subluxation of the toes leads to their progressive defunctioning for weight bearing and commonly causes pressure problems as they rub against the shoe uppers. In addition, the specialized weight-bearing skin and subcutaneous tissue lying under the metatarsal heads is drawn forward to be replaced by unprotected skin, which becomes hyperkeratotic in response to repeated loading. The resulting plantar callosities exacerbate the pain of metatarsalgia and may require regular chiropody. Hallux valgus almost invariably develops as a consequence of the spreading of the forefoot and the bowstring effect from the extensor hallucis longus.

Involvement of the ankle joint in isolation is rare but may occur in association with disease of the subtalar and midtarsal joints, which occurs in two-thirds of patients. Valgus deformity of the hindfoot is usual and may be exacerbated by rupture of the tibialis posterior tendon which buttresses the medial aspect of the ankle. Associated collapse of the medial longitudinal arch of the foot may add to the resulting mechanical problems, which include severe pain around the lateral aspect of the ankle from joint compression. Extensive synovitis, particularly of the long flexor tendons, may lead to compression of the medial plantar nerve in the tarsal tunnel.

Fig. 5 Forefoot deformity is common from an early stage of rheumatoid arthritis as a result of destruction of the normal transverse arch by synovitis of the metatarsophalangeal joints.
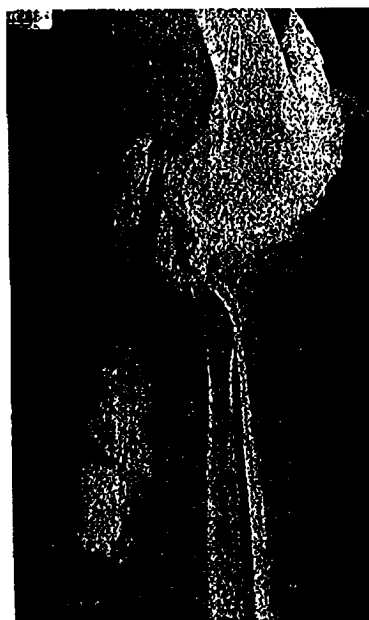

Fig. 6 Ultrasound of a large popliteal cyst communicating with the knee joint (left). This technique has superseded arthrography (right) and the neck of the cyst (arrowed) communicating with the joint is clearly seen.

Knees

Involvement of the knee is an important and relatively common cause of disability from an early stage in the disease because of its role in load bearing. Synovial proliferation is usually most obvious in the suprapatella pouch and there may be pronounced wasting of the quadriceps as a result of reflex muscle inhibition. Synovial effusion typically produces posterior knee pain in the early stages by stretching the posterior capsule of the joint. This may lead to the development of a popliteal cyst communicating with the joint via a valve-like opening which does not easily allow fluid back into the joint. Rupture of the joint or a popliteal cyst may cause extravasation of highly irritant synovial fluid into the calf where the inflammation and swelling may mimic a deep vein thrombosis. These two pathologies can sometimes coexist because there may be partial obstruction to the venous return by the presence of an extensive popliteal cyst (Fig. 6). It may be necessary to investigate both diagnoses by ultrasound and phlebography.

Tricompartmental damage to the articular surfaces of the knees is the usual outcome of late disease and may cause severe instability of the joint as the collateral and cruciate ligaments become lax. Valgus deformities of the knees are the usual consequence of loading such unstable joints, and are often combined with a degree of fixed flexion deformity. Pain may also arise from periarticular structures, such as the insertion of the collateral ligaments which are chronically under strain in the unstable knee joint. Even in the end stages of destruction of the knee joint it may be possible to afford the patient considerable relief by attention to specific anatomical sites of injury.

Hips

Involvement of the hips in rheumatoid arthritis is relatively uncommon overall (c. 25 per cent) but is a major source of morbidity in those patients with more severe diseases who tend to make up the hospital outpatient population. Pain is usually experienced in the groin and the buttock but may radiate to the knee, sometimes mimicking knee arthritis. Rotation and abduction of the hip are reduced before flexion, but ultimately fixed flexion deformity of the joint may occur. Even in patients with advanced hip arthritis a considerable contribution to the pain may come from periarticular tissues, in particular trochanteric bursitis. Typically, this is associated with tenderness over the greater trochanter (which may stop the patient lying on that side), and pain on adduction of the hip which may be referred to the lateral aspect of the knee. In late disease these may be relatively sudden collapse of the femoral head, with a severe increase in pain and disability, necessitating joint replacement.

AXIAL SKELETON

In contrast to the spondyloarthropathies, involvement of the sacroiliac joints is rare in rheumatoid arthritis. However, spinal arthritis is common, up to 80 per cent of patients demonstrating radiological evidence of the disease in the cervical spine. This may be asymptomatic but the most frequent result is painful limitation of movement, often in several planes. The most common radiological abnormalities consist of osteoporosis, erosion of the zygapophyseal joints, erosions of the vertebral end plates, and loss of disc space in the absence of florid osteophytosis.

There may be evidence of atlantoaxial subluxation in up to 25 per cent of patients attending hospital, but less than one in four of these will be symptomatic. In the normal joint the odontoid peg is closely opposed to the posterior aspect of the anterior arch of the atlas by a network of ligaments, including the cruciate, posterior longitudinal, and alar ligaments. Instability of the atlantoaxial joint results from erosion of the odontoid peg or rupture of the supporting ligaments and will be apparent on lateral radiographs of the cervical spine taken in flexion and extension. Lateral or vertical subluxation of the atlantoaxial joint may also occur. Separation of the odontoid peg from the arch of the atlas by 4

mm or more is abnormal. The risk of cord compression is greatest in males, in those with a subluxation exceeding 8 mm, and where there is also vertical subluxation of the atlantoaxial joint. Minor degrees of atlantoaxial subluxation can be relatively well tolerated because the cervical canal is relatively wide at this level. Subaxial subluxation presents a serious risk of cord compression because the cervical canal there is narrower.

Serious erosive change in the cervical spine is more likely in patients who have pronounced peripheral joint disease and in those on corticosteroids. Erosions, when present, usually develop within 2 years of the onset. Symptoms suggestive of atlantoaxial disease include high cervical pain radiating to the occiput and temporal regions, exacerbated by neck movements. There may be audible or palpable clunking on flexion, and inability to place the chin on the sternum is a useful screening test. At its worst, compression of the cervical cord or vertebral blood vessels may lead to quadriplegia or sudden death. More commonly it causes shooting pains in the arms or legs, weakness, and unsteadiness of gait or sphincter disturbance. A mild spastic weakness in the arms or legs may be difficult to detect in a patient whose limbs have already been rendered weak and stiff by arthritis, but pathologically brisk tendon jerks, a positive Hoffman sign, or upgoing plantar response are important signs. Loss of proprioception, vibration sense, and balance may indicate significant damage to the posterior columns, but can be difficult to distinguish from the peripheral neuropathy that is common in rheumatoid arthritis.

Acute subluxation of the cervical spine with neurological signs will initially require immobilization with skeletal traction. A proportion of cases will improve with such conservative measures but most will be left with marked residual neurological impairment and handicap. It has been estimated that atlantoaxial subluxation is responsible for as many as 5 per cent of all deaths in rheumatoid arthritis. However, although there may be pre-existing radiological evidence of atlantoaxial subluxation in a small proportion of these, it is rare for overt cervical myelopathy to have developed. The most common indication for fusion is intractable pain, and it is notoriously difficult to predict individuals at risk of catastrophic neurological damage on the basis of symptoms and physical examination alone. Patients with atlantoaxial slip of 8 mm or more should certainly be considered for posterior fusion, particularly if there is also evidence of vertical migration of the joint or if neurological signs suggestive of myelopathy are present. Magnetic resonance imaging provides an accurate, non-invasive method of assessing the degree of compromise to the spinal cord that can be particularly useful in patients with subaxial subluxation (Fig. 7).

Other joints

Hoarseness of the voice may occasionally be caused by effusion within the cricoarytenoid joints. Temporomandibular joint disease causes pain on chewing and may particularly restrict opening of the mouth. Discitis can occur in the lumbar as well as the cervical spine.

EXTRA-ARTICULAR FEATURES

The majority of patients with rheumatoid arthritis exhibit at least some extra-articular features and these tend to be more numerous and more severe in those with high titres of rheumatoid factor in the blood. However, these systemic features are highly variable, ranging from the fairly trivial (e.g. episcleritis, subcutaneous nodules) to the potentially life-threatening (e.g. systemic vasculitis, pleuropericarditis). Actuarial studies indicate that rheumatoid arthritis significantly reduces life expectancy. This is not explained by the effects of progressive immobility alone but by the systemic nature of the illness. Long-term studies suggest that rheumatoid arthritis itself is either responsible directly or contributes to death in about one-third of patients. This effect appears to be particularly pronounced in seropositive middle-aged men with pronounced extra-articular features.

The extra-articular disease may pursue a course quite dissociated from the joint disease. For example, systemic vasculitis may appear for the first time when joint synovitis has been suppressed by disease-modifying drugs.

The precise cause of many of the extra-articular features of rheumatoid arthritis remains to be elucidated. However, three major pathological phenomena dominate the disease: inflammation of membranes (pleura, pericardium, and others as well as the synovium), nodule formation, and vasculitis. Nodules correlate with titres of IgM rheumatoid factor, and vasculitis appears to depend more on the formation of IgG-containing immune complexes. Combinations of these phenomena explain most extra-articular events.

Rheumatoid nodules

Subcutaneous and intracutaneous nodules are a hallmark of the disease, occurring in about one-quarter of patients. They are discrete, firm, non-tender swellings varying from a few millimetres to several centimetres in size, and in rare instances, usually seropositive males, they may occur in the absence of typical articular disease (rheumatoid nodulosis). They occur most frequently on the extensor surface of the forearm and olecranon, sites where repeated minor trauma from leaning could initiate their formation. They also commonly occur around tendons, including the Achilles, the flexor and extensor tendons of the fingers, and over the sacrum. Sometimes superficial nodules may break down with ulceration of the surrounding skin.

Histological examination of these nodules reveals central fibrinoid necrosis surrounded by palisades of fibroblasts and chronic inflammatory cells, suggesting a combination of proliferative and destructive tissue responses.

Rheumatoid nodules may also develop in many other tissues including the eye (scleromalacia), pleura, pericardium, and parenchyma of the lungs and heart (where they may be found at autopsy in as many as 10 per cent of patients). They sometimes occur on the vocal cords and very occasionally they may cause dysfunction of the heart valves or conducting tissue. The Caplan syndrome, describing the combination of massive pulmonary fibrosis and pulmonary nodules, was first described in miners with rheumatoid arthritis but it may also develop, following occupational exposure to inorganic dusts (e.g. silica, asbestos), in seropositive individuals without arthritis. Such intrapulmonary nodules may be mistaken for other pathology, including tumours or abcesses, particularly if they break down and cavitate.

Fig. 7 Sub-ascial subluxation of the cervical spine (C 5/6) with compression of the spinal cord. The loss of disc height and subluxation in the absence of marked osteophytosis on the standard radiographs (left) is typical of rheumatoid arthritis. Magnetic resonance imaging (right) reveals the extent of the spinal cord compression.

Anaemia

A moderate normochromic normocytic anaemia is an almost invariable finding in active rheumatoid arthritis and appears to be multifactorial in origin. A number of factors related to the inflammatory process probably contribute to this anaemia. Iron may be sequestered in an unusable form (haemosiderin) by the reticuloendothelial system; there may be ineffective erythropoiesis and red blood cell survival is reduced; haemodilution may occur as a result of increased blood volume. The potential influence of increased levels of cytokines (interleukin-1 and interleukin-6) and blunted erythropoietin responses are the foci of considerable research interest. The potential therapeutic role of recombinant erythropoietin has not yet been established.

The most important practical consideration is the differentiation of iron-deficiency anaemia secondary to gastrointestinal haemorrhage from the anaemia of chronic disease. This may be particularly difficult when the two coexist. As a general rule, a microcytic hypochromic blood picture indicates iron deficiency anaemia and should be treated and investigated as such. In the chronic anaemia of rheumatoid disease the blood picture is usually normocytic and normochromic or hypochromic (but rarely microcytic). Assessment of the bone marrow iron stores is the most reliable indicator of iron deficiency but is rarely necessary if the mean corpuscular volume, serum iron-binding capacity, and ferritin are used in combination. Iron-binding capacity is typically reduced in active rheumatoid arthritis; normal or slightly raised levels in the presence of a low serum iron are therefore highly indicative of iron deficiency. In contrast, as part of the acute phase response, ferritin levels are typically elevated in active rheumatoid arthritis unless there is iron deficiency. The typical anaemia of chronic disease seen in rheumatoid arthritis correlates closely with the sedimentation rate as a marker of disease activity and does not respond to iron, folic acid, or vitamin B_{12}. In contrast, suppression of the disease by corticosteroids appears to mobilize iron stores rapidly, resulting in increased haemopoiesis and a subsequent rise in haemoglobin concentration.

Platelets

The platelet count is commonly increased to levels greater than 5×10^5 in active disease and this may also occur when there is active bleeding from the intestine. In contrast, the platelet count may be low in the Felty syndrome or as a result of marrow toxicity from antirheumatic drugs.

Vasculitis

Vascular lesions are evident at autopsy in as many as 25 per cent of individuals with rheumatoid arthritis, with an equal sex-incidence. Many different sizes of blood vessels may be affected. The resulting clinical spectrum of disease is therefore highly variable. Intimal hyperplasia of the small terminal digital vessels causes very limited cutaneous lesions (nailfold infarcts, rashes, and splinter haemorrhages) and has a generally good prognosis in the absence of other signs suggestive of more severe systemic involvement. In contrast, severe life-threatening systemic tissue infarction (widespread cutaneous ulceration, infarction of the bowel, mononeuritis multiplex) may develop if there is involvement of the larger blood vessels by leucocytoclastic or necrotizing vasculitis. This may be indistinguishable from polyarteritis nodosa with fibrinoid necrosis of the intima and infiltration of the outer layers by lymphocytes and occasional polymorphonuclear leucocytes.

Vasculitis is more common in patients with high levels of IgM rheumatoid factor and severe joint disease, although the activity of the synovitis and extra-articular disease is often temporally dissociated. Its incidence increases with the duration of the disease, but occasionally it may be present from the outset, even, rarely, in the absence of joint disease. It is possible that the vasculitis may be initiated by IgG rheumatoid factor containing immune complexes deposited in the vessel walls, since these can activate complement. Vasculitis is increased somewhat in patients in whom antinuclear antibody can be detected and correlates more closely with raised circulating levels of IgG than IgM rheumatoid factor. In some patients with vasculitic features there may be detectable

circulating cryoglobulins and low concentrations of complement in plasma.

Rheumatoid vasculitis is associated with significant mortality but this can be significantly reduced with appropriate therapy. Oral or intravenous pulses of corticosteroids alone are probably ineffective in the long term; indeed some observers have suggested that the reduction in the incidence of rheumatoid vasculitis since the 1960s can be attributed to the reduced use of steroids. However, regimens based on intermittent boluses of cyclophosphamide coupled with corticosteroids appear to induce effective and sustained suppression similar to that obtained in other forms of necrotizing vasculitis.

Lung involvement

Several patterns of lung disease may occur:

Pleurisy has an incidence of about 1 per cent overall, but pleural effusions due to rheumatoid arthritis may go undetected. Pleural involvement is five times more common in men than in women and often needs differentiation from other causes, particularly when other systemic features, such as weight loss and fever, are present. The fluid has raised protein, low glucose, and low complement levels and is typically positive for rheumatoid factor. The cell count is high due to the presence of lymphocytes, macrophages, and, to a lesser extent, multinucleate giant cells, including comet cells. Pleural biopsy may reveal rheumatoid granulomata, like an 'opened-out rheumatoid nodule', but typically there is the appearance of non-specific inflammation which does not allow differentiation from other causes of pleurisy.

Nodules are more common in the upper than the lower zones and may be single or multiple. Cavitation may occasionally lead to haemoptysis, and tissue diagnosis can usually be obtained by percutaneous or transbronchial needle biopsy without recourse to thoracotomy.

Pulmonary fibrosis is common in rheumatoid arthritis but is often subclinical. Ten per cent of patients have radiological evidence of fibrosis and many more have evidence of impaired vital capacity and gas transfer. Classical fibrosing alveolitis occurs in 2 per cent of patients with rheumatoid arthritis and causes progressive dyspnoea, clubbing of the fingers, fine late-inspiratory crepitations, and lower-zone reticulonodular shadowing on the chest radiograph. It carries a 5 year mortality of 50 per cent and responds poorly to treatment with corticosteroid, D-penicillamine, or cytotoxic agents.

Obliterative bronchiolitis is a rare but rapidly progressive and fatal process manifesting with an acute onset of breathlessness. Widespread small airways obstruction is present in the absence of alveolar fibrosis and there is little evidence of inflammation.

Many patients with rheumatoid arthritis have evidence of airways obstruction irrespective of their smoking habits. Bronchiectasis also appears to be more common in those with the disease and to predate its onset.

Cardiac involvement

This is more common in men and is frequently subclinical. Small pericardial effusions can be found by ultrasonography in up to half those patients with seropositive nodular disease admitted to hospital but this represents the severe end of the disease spectrum. The true overall prevalence is probably between 5 and 10 per cent. Clinically symptomatic pericarditis has an annual incidence of about 0.4 per cent and may occur at any stage of the disease. However, potentially life-threatening complications such as tamponade or constrictive pericarditis are very rare.

Valvulitis may be apparent at autopsy in 20 per cent of cases but is rarely symptomatic during life. Granulomatous thickening of the cusps of the aortic valve occurs more frequently than in the mitral valve but only rarely produces incompetence of the valve. Acute aortic regurgi-

tation following perforation of one of the cusps is described and may need emergency valve replacement.

Autopsy studies reveal a patchy myocardial fibrosis in about one-sixth of patients and myocardial nodules can be found in some patients. Although evidence of a small-vessel vasculitis may be apparent at post-mortem in 20 per cent of patients, the incidence of myocardial infarction resulting from necrotizing vasculitis during life seems to be very low. However, there is an excess cardiac mortality among patients with rheumatoid arthritis that appears to be caused through ischaemic heart disease, although the precise mechanisms involved are not clear.

Eye involvement (see Section 26)

This is common in rheumatoid arthritis and may be due to localized tissue involvement or as part of a more generalized disorder involving the exocrine glands—Sjögren's syndrome. Exceptionally there may be diplopia resulting from stenosing tenosynovitis of the superior oblique tendon (Brown's syndrome).

Sjögren's syndrome is characterized by diffuse infiltration of the exocrine glands and other tissues by lymphocytes, resulting in destruction and glandular insufficiency (see Chapter 18.11.5). The syndrome occurs in one-fifth of patients with rheumatoid arthritis (secondary Sjögren's syndrome).

Typical symptoms consist of pain, erythema and grittiness in the eyes, photosensitivity, and stickiness associated with adherent strands of mucus. Secondary bacterial infection is relatively common due to the loss of lysozymes, bacteriostatic agents normally present in tears. Corneal damage may occur.

Extraglandular involvement is less common in secondary Sjögren's syndrome than in the primary disease, but half of those with rheumatoid arthritis exhibit at least some degree of parotid gland enlargement. General malaise is common and cutaneous vasculitis, peripheral neuropathy, renal tubular acidosis, interstitial pulmonary fibrosis, and myositis may all coincide. Lymphoproliferation occurs in one-quarter of all patients (particularly those with primary disease), and there is a measurable excess of individuals who subsequently develop lymphoma.

In difficult cases the diagnosis may be aided by the following: lymphocytic infiltration of labial salivary glands on biopsy; the presence of anti-salivary gland antibodies; reduced secretion of saliva measured by cannulation of the parotid or submandibular ducts; abnormalities of the parotid ductular architecture at sialography. Rheumatoid factor is almost invariably positive and 70 per cent of patients are also positive for anti-nuclear factor.

Episcleritis usually appears as a raised lesion in the anterior sclera with hyperaemia of the deeper layers. The lesions are often transient but may be associated with vasculitis elsewhere. Low-grade discomfort is not uncommon and may require the use of topical corticosteroids.

Scleritis is less common but potentially more serious since it may lead to progressive thinning of the sclera (scleromalacia) and even perforation. Treatment with systemic corticosteroids is usually required. Keratolysis (corneal melting) and limbal guttering are rare complications of vasculitis of the circumcorneal vessels which can also cause perforation.

Peripheral nerve involvement

This is common in rheumatoid arthritis but is quite frequently masked by the severity of the joint disease. Entrapment neuropathies have already been considered and are amendable to treatment by corticosteroid injection and other measures to relieve local pressure.

A mild glove and stocking sensory neuropathy is relatively common in rheumatoid arthritis but is usually benign and does not imply inflammation of nervous tissue. However, there may be lymphocytic infiltrates of the dorsal root ganglia in Sjögren's syndrome. In contrast, the presence of a mixed sensorimotor neuropathy or mononeuritis multiplex is indicative of underlying vasculitis of the vasa nervorum and dictates the

use of high-dose corticosteroid therapy with cyclophosphamide as out-lined above.

Muscle involvement

In rheumatoid arthritis muscle involvement is usually attributed to the reflex inhibition and wasting resulting from severe joint pain. Focal lymphocytic infiltration may be present on muscle biopsy, but its relevance to symptoms is in doubt and there is no increase in muscle enzyme concentrations in the serum to suggest active myositis in all but a tiny minority of patients. It is important to remember that some drugs used in the treatment of the disease may cause a myopathy (e.g. cortico-[j]steroids, antimalarials) and that D-penicillamine is well documented to cause myasthenia gravis in some patients.

Liver involvement

This is evident in about 10 per cent of patients with active disease. There may be mild hepatosplenomegaly and asymptomatic elevation of the serum alkaline phosphatase but liver biopsy rarely shows specific changes. Minor degrees of fatty change, Kupffer cell hyperplasia, and lymphocytic infiltration of the portal tracts may be seen. The potential hepatotoxicity of many drugs used in the treatment of rheumatoid arthritis should be recalled, particularly high-dose salicylates, sulphasalazine, gold salts, and antimalarials.

Renal involvement

This is less of a problem in rheumatoid arthritis than might be expected from analogy with other disorders associated with vasculitis, such as systemic lupus erythematosus and polyarteritis nodosa. Renal biopsy studies have consistently failed to reveal evidence of renal vasculitis. Renal papillary necrosis and interstitial nephritis occasionally occur and are probably related, at least in part, to the use of non-steroidal analgesics (see Section 20). IgA nephropathy associated with elevated serum levels of IgM and IgA is described in rheumatoid arthritis but is probably no more common than in age-matched controls.

Gold salts and D-penicillamine can cause proteinuria due to membranous glomerulonephritis in about 10 per cent of patients. This may persist for up to 2 years after the drug has been stopped but rarely progresses to frank nephrotic syndrome.

Bone involvement

This occurs in the vicinity of the joints, where juxta-articular osteoporosis is an early feature. It also occurs as a more generalized phenomenon, partly as a result of the relative immobility of patients with severe arthritis but particularly in those receiving corticosteroids. Osteoporotic fractures are common and may occur at sites such as the pubic rami or ankle where they mimic exacerbations of the joint disease. Fractures of the long bones may develop with minimal trauma and are particularly common where there is pre-existing angular deformity of the limb (Fig. 8). A small proportion of patients may develop osteomalacia. However, its prevalence in patients with rheumatoid arthritis is probably no greater than in similarly handicapped, age-matched populations who also receive little exposure to direct sunlight and have diets poor in vitamin D.

The Felty syndrome

Lymphadenopathy is common in patients with rheumatoid arthritis, biopsies showing nodular hyperplasia. It is most obvious in patients with the Felty syndrome (rheumatoid arthritis, splenomegaly, and leucopenia). Other extra-articular features are frequently present and include anaemia, thrombocytopenia, persistent vasculitic leg ulceration, cutaneous pigmentation, weight loss, and recurrent infection. It is uncommon (less than 1 per cent of all cases) and rarely develops in patients who have had the disease for less than 10 years. It also seems to be particularly uncommon in certain ethnic groups, including Greeks and Chinese. This may reflect the weaker association of rheumatoid arthritis with the Dw4 antigen in these populations, since this marker is present in about 85 per cent of individuals with the Felty syndrome in the United Kingdom.

Susceptibility to recurrent infection is closely related to the absolute neutrophil count, which may be less than $100/mm^3$. Antineutrophil antibodies may be detected in a proportion of cases, but the pathogenesis of the Felty syndrome is uncertain. Inadequate granulopoiesis, sequestration in the bone marrow, excessive margination of the circulating polymorphonuclear leucocytes, and destruction in the spleen have all been invoked. Splenectomy usually results in a temporary increase in the neutrophil count but does not provide reliable protection against recurrent infection. It is probably best reserved for those cases in which severe anaemia is due to hypersplenism. The potential role of recombinant granulocyte colony stimulating factors is interesting but remains to be evaluated.

CLINICAL COURSE OF THE DISEASE

The outcome of rheumatoid arthritis is unpredictable and observations in hospital populations are an unreliable guide to the clinical picture in the disease overall. Many patients with mild disease are never referred to hospital and may run a relatively benign, self-limiting course. Ten-year follow-up of patients admitted to hospital suggests that 25 per cent will remain fit for most activities, 40 per cent will exhibit moderate functional impairment, 25 per cent will be severely disabled, and 10 per cent will be wheelchair-bound.

An adverse outcome is suggested by an insidious, progressive onset of the symptoms, pronounced extra-articular disease (including nodules), the early development of erosions and failure to respond adequately to anti-inflammatory analgesics. Relatively severe disease also correlates with the presence of high titres of circulating rheumatoid factor and the presence of the HLA-DR4 antigen (particularly DR4 homozygosity). Although it is standard practice to begin treatment at an early stage in patients with more aggressive joint disease, evidence that this approach really does have a major influence and modifying effect on the long-term degree of disability and handicap is equivocal.

Fig. 8 Osteoporotic fracture of the tibia in a patient with severe arthritis of the knee joint and consequent angular deformity. The patient continued to walk on the leg for several weeks with increasing pain before seeking medical assistance.
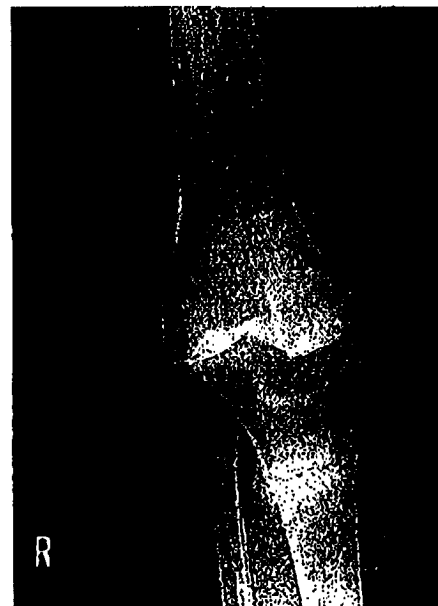
COMPLICATIONS

Septic arthritis (see Chapter 18.9) is a serious complication of rheumatoid arthritis, with a mortality rate of 25 per cent in some series. It is typically monoarticular but may be polyarticular in a quarter of cases. The expected clinical features (fever, rigors, neutrophil leucocytosis, and local inflammation of the joint) are frequently blunted or absent. Staphylococci account for three-quarters of all infections and may cause very rapid destruction of the articular surface if left untreated. In addition to systemic antibiotics, daily aspiration of the purulent synovial fluid at least is required. Open surgical drainage is sometimes necessary, particularly if the diagnosis has been delayed.

Rheumatoid arthritis is the commonest cause of AA amyloidosis in the United Kingdom (see Chapter 11.13.1). Its prevalence on rectal biopsy may be as high as 5 per cent, but rapidly progressive disease is very unusual. Suppression of disease activity with disease-modifying agents is probably as effective as the use of cytotoxic agents, although chlorambucil may be effective, particularly in juvenile rheumatoid arthritis and Still's disease.

DIFFERENTIAL DIAGNOSIS

When present in its mature, classical form the diagnosis of rheumatoid arthritis presents few problems. However, particularly during the early stages it may be difficult to distinguish from other, sometimes self-limiting, inflammatory arthropathies. For this reason it is probably best to be guarded about the diagnosis if there is any significant doubt. This is particularly true when rheumatoid factor is absent.

Viral infections are commonly associated with transient arthralgias and sometimes more prolonged attacks of synovitis. Numerous types of bacterial infection may also be followed by reactive arthropathies, and serological tests may confirm recent infection. These syndromes can usually, but not invariably, be distinguished from rheumatoid arthritis by the history, but a strongly positive test for rheumatoid factor is undoubtedly the most useful discriminatory laboratory test. In practice it is rare for there to be much difficulty distinguishing the seronegative spondarthropathies from rheumatoid arthritis, with the exception of psoriasis. This may be associated with an identical arthritis to seronegative rheumatoid arthritis and may sometimes develop before skin lesions (psoriatic arthritis without psoriasis) although there is usually a family history in such cases. Peripheral joint involvement in ankylosing spondylitis may be confusing, particularly in children, in whom it frequently antedates overt spinal disease. However, the asymmetrical pauciarticular lower limb distribution contrasts starkly with the polyarticular distribution typical of juvenile-onset rheumatoid arthritis.

Widespread synovitis commonly occurs in systemic lupus erythematosus but, although joint deformities may develop, bony erosion is very unusual. Rheumatoid factor is often present in low titre in addition to antinuclear antibodies, but evidence of renal disease, photosensitivity, mouth ulcers, pleuropericarditis and the presence of anti-DNA antibodies should clarify the diagnosis.

About 10 per cent of patients with gout have polyarticular disease from the outset but this tends to have an asymmetrical distribution and a predilection for the lower limbs, in particular the great toe. Negative tests for rheumatoid factor plus the demonstration of an elevated plasma urate level are suggestive, but the demonstration of urate crystals within the affected joints provides the definitive test. Gout may also preferentially affect joints involved by osteoarthritis, causing discrete episodes of inflammation. These, and osteoarthritis itself, can usually be distinguished without too much difficulty. However, rheumatoid arthritis superimposed on osteoarthritis can be difficult unless there are raised titres of rheumatoid factor.

The several forms of juvenile chronic arthritis can usually be distinguished from juvenile-onset rheumatoid arthritis by the absence of rheumatoid factor and the distinctive pattern of joint involvement. Still's disease has a systemic onset with fever, neutrophilia, rash, lymph-

adenopathy, and hepatosplenomegaly. Rheumatoid factor is absent and the systemic features of the disease may predate the onset of joint symptoms by weeks or even months. It is uncommon in adults but may cause severe systemic upset requiring extensive investigation to exclude other connective tissue disorders, sepsis, or malignancy.

Management

Effective management of the patient with any but the mildest form of rheumatoid arthritis requires a multidisciplinary approach usually co-ordinated by a rheumatologist. Accurate diagnosis is essential for the early application of appropriate forms of therapy, the education of the patient in joint protection, and for counselling in adapting to disability and planning adequate social support.

In addition to standard pharmaceutical preparations, there are many other options for amelioration of symptoms, some orthodox and others not. Most patients seek relief from proprietary medicines and heterodox treatments such as copper bracelets, acupuncture, and various dietary regimes at some time in their illness. The value of many of these has undergone little rigorous testing but should not be discounted entirely.

The value of physical measures is well established. Acutely inflamed joints benefit from rest which may be accomplished either with bedrest or splintage of the affected joints, depending on the clinical context. Local application of heat or cold to affected joints and gentle massage are also frequently effective, and can be combined with stretching exercises to prevent the development of deformities consequent upon tendon and joint contractures. Regular exercise to strengthen muscles can help to stabilize damaged joints and should be initiated as early in the disease as practicable to prevent excessive muscle wasting. Many varieties of supporting splints are available to allow patients to continue to use joints that have been rendered painful or unstable by arthritis, and access to good orthoses may revolutionize the life of a patient, even with severe disease. In particular, careful attention to footwear with the provision of 'depth' shoes with soft uppers and adequately supporting insoles is important, both for immediate comfort and the prevention of future deformities.

Patients with more severe disabilities often benefit greatly from a careful assessment of the home environment, with advice on how to save labour and the provision of aids to give a mechanical advantage for specific tasks. Wheelchairs are often viewed negatively by patients and doctors alike but may greatly increase the range of activities and mobility open to the patient, thereby reducing the potential for social isolation.

DRUG TREATMENT

The dominant complaints of most patients from an early stage in the disease are pain and stiffness. These can arise as a mechanical phenomenon in damaged joints as well as from the primary inflammatory process. Analgesics ('first-line drugs') are therefore relevant at all stages of the disease. In contrast, the use of disease-modifying agents ('second-line drugs') is most logically restricted to those patients with potentially reversible soft-tissue inflammation and early erosive damage. 'Third-line drugs' include various cytotoxic agents and corticosteroids.

First-line drugs

These should include simple analgesics, such as paracetamol, codeine, and dextropropoxyphene. If these are effective, they should be used in preference to other non-steroidal anti-inflammatory drugs (NSAIDs) because of their relative safety. Many patients with mild or quiescent disease may require only intermittent analgesia.

A large number of NSAIDs are available with a broadly similar pattern of efficacy and side-effects, but there may be differences in response between individual patients. Many of the newer variants have prolonged half-lives which give a more sustained action, even allowing a single

daily dosage regimen. Others may rely on sustained slow-delivery systems to achieve the same effect, despite the relatively short half-life of the drug being administered. It is logical to develop familiarity with a small selection of these drugs, including representatives from different chemical groups (Table 3). It is most appropriate to prescribe only one drug at a time and to use an adequate dose before abandoning it as ineffective. The use of nocturnal suppositories (indomethacin, diclofenac, naproxen) for the relief of morning stiffness is one particular exception to this general rule. Before embarking on long-term administration of these drugs it should be clear that there is a definite benefit to the patient, and the requirements for these drugs in the light of varying disease activity and symptoms should be critically reviewed periodically. The potential for serious adverse side-effects should not be underestimated. Gastrointestinal problems alone are very common, particularly as a result of superficial mucosal erosion, which may cause dyspepsia and haemorrhage. The relationship with chronic gastroduodenal ulceration is less clear-cut but it is important to remember that almost half of all patients admitted to hospital with acute gastrointestinal bleeding are taking non-steroidal anti-inflammatory drugs.

Second-line drugs

These are believed to exert an influence on the underlying pathological processes involved in rheumatoid arthritis. In contrast to the first-line drugs, they may retard the progression of erosive joint damage, but their effects are not usually apparent until they have been taken for at least 2 to 3 months. Commonly used second-line drugs include gold salts, D-penicillamine, antimalarials (hydroxychloroquine), and sulphasalazine. They are most appropriately used in patients who have evidence of widespread synovitis with inadequate control of symptoms by first-line drugs. Patients with advanced secondary degenerative changes and mechanical deformity are unlikely to respond to this form of therapy. Highly active disease limited to one or two joints may be best managed in the first instance by local measures, such as intra-articular corticosteroid injection, splintage, or synovectomy (surgical or radiochemical).

The effectiveness of these second-line agents can be monitored not only by the demonstration of improvement in such clinical parameters as pain, morning stiffness, and grip strength, but also by a fall in the sedimentation rate, platelet count, level of rheumatoid factor and acute-phase reactants. They should only be continued where a clear beneficial effect can be demonstrated after an adequately prolonged trial, because of the wide range of potential ill-effects. These include skin rashes, bone-marrow toxicity, and mouth ulcers (with gold, D-penicillamine, and sulphasalazine), nephrotic syndrome (gold and D-penicillamine), hepatitis ((gold and sulphasalazine), and retinopathy (antimalarials). Accordingly, careful monitoring (e.g. urinalysis, full blood count, and liver function) for side-effects is essential when these drugs are prescribed, an important responsibility of the clinician instigating the therapy even if not responsible for prescribing.

After 1 year, about two-thirds of patients started on second-line drugs will be doing well, while the remainder will have stopped the drug because of side-effects or lack of efficacy.

Third-line drugs

These include azathioprine, cyclophosphamide, chlorambucil, and methotrexate, all of which can modify the course of rheumatoid arthritis. Low-dose methotrexate (7.5–15 mg weekly), in particular, has found a firm place in treatment, and in many centres is used frequently as a second-line agent. In low dose it does not have the hepatotoxicity otherwise associated with its use; bone-marrow suppression is uncommon, but occasionally severe episodes of pneumonitis occur.

Corticosteroids are highly potent inhibitors of the inflammatory response that can have dramatic effects on the synovitis of rheumatoid arthritis. Unfortunately the plethora of unwanted side-effects (osteoporosis, fluid retention, atrophy of the dermis, increased susceptibility to infection) strictly limits their usefulness. Nevertheless about a quarter of hospital outpatients ultimately receive corticosteroids, usually in doses less than 10 mg daily, and such an approach may be highly effec-

Table 3 *Chemical groupings of the non-steroidal anti-inflammatory analgesics*

Phenylacetic acids (propionic acids)	Ibuprofen, fenoprofen, ketoprofen, flurbiprofen
Indoleacetic acids	Indomethacin, sulindac
Heterocarboxylic acids	Aspirin, salicylsalicylic acid, diflunisal
Naphthaleneacetic acids	Naproxen
Oxicams	Piroxicam, tenoxicam
Pyrazolidinediones	Phenylbutazone, oxyphenbutazone

tive in keeping patients mobile and independent when other drugs have failed.

A number of forms of experimental therapy have proved of some benefit in the treatment of rheumatoid arthritis, although their use is restricted to a few centres. These include total lymphoid irradiation, thoracic duct drainage, anti-CD4 monoclonal antibodies, and antibodies directed against the lymphocyte cell-surface determinant, CDw52.

SURGERY

Many aspects of the disease are amenable to surgical correction, and access to good orthopaedic services is critical to its management. The main indications for surgical intervention are to relieve pain, to correct deformity, to reduce instability, and to increase the effective range of movement and function.

Soft-tissue procedures

These include the repair of ruptured tendons, tendon transfers, decompression (carpal tunnel), or transfer of nerves (ulnar nerve at the elbow).

Synovectomy

This can be a useful procedure in joints with persistent active synovitis, particularly when the damage to the articular surface is relatively mild. It is also frequently performed in conjunction with excision arthroplasties (proximal radial head, lower end of ulna, forefoot arthroplasty).

Arthrodesis

This still plays a useful role in the surgical management of arthritis despite the loss of movement that it necessarily produces. It is particularly useful for the painful wrist or finger, and can correct pain and instability in the ankle and thumb. Fusion of the cervical spine may be essential to prevent catastrophic neurological damage to the cervical spinal cord.

Joint replacement arthroplasty

This has revolutionized the treatment of patients with severe arthritis of the large, weight-bearing lower limb joints. Total hip replacement is successful in 95 per cent of individuals, although ultimately revision due to loosening of the prosthesis and pain may be necessary. For this reason it is wise to consider using an uncemented prosthesis in individuals under the age of 60. Thromboembolism in the postoperative phase is rare in patients with rheumatoid arthritis compared to those with osteoarthritis. Sepsis occurs occasionally and can be a disastrous complication which may require removal of the prosthesis. The introduction of partially constrained total condylar prostheses for the knee has increased the success from replacement of this joint to rates similar to those of the hip although postoperative mobilization and recovery tends to be a little slower.

Replacement of other joints such as the elbow and shoulder may be highly successful in many patients but is less predictable. It should therefore be reserved for individuals with severe pain and limitation of movement. Prosthetic replacement of the wrist and ankle is not yet satisfactory and pain relief is better achieved in most cases by arthrodesis.

18.6 Osteoarthritis

C. W. Hutton

Osteoarthritis is an enigmatic condition. Fatalism about the process being simply due to 'wear and tear' and old age has delayed systematic study. However, present knowledge of osteoarthritis allows a more rational approach to its management, underlines its importance as a public health problem, and delineates the directions for future research.

The concept of osteoarthritis

As osteoarthritis is poorly understood, it is difficult to define. Some features are recognized as important in diagnosis but whether they are necessary or sufficient remains controversial. Historically, it was recognized from morbid anatomy and later radiographic changes. Some forms of arthritis were characterized by loss of articular cartilage associated with bone increase ('hypertrophic'), in contrast to that associated with bone loss ('atrophic'). With the recognition of the role of chronic infection and the evolution of the diagnosis of inflammatory arthritis the 'atrophic' group became well defined. A rump of 'disease' remained associated with bone proliferation that can loosely be described as osteoarthritis. The age association and premature development of osteoarthritis after trauma meant that it was seen as a degenerative process, resulting in the delineation of 'degenerative joint disease'.

Osteoarthritis is a chronic condition, and although it may develop acutely, its evolution usually takes years. Current knowledge is primarily based on observations made at a single time in the evolution of the disorder. In humans, short-term follow-up studies are few and long-term studies exceptional. Any understanding of the mechanism of osteoarthritis must take account of its key features, which include: age association, the pattern of joint involvement, the common homogeneous features, and the contrasting marked heterogeneity.

A current pathological definition of osteoarthritis is 'a disease process of synovial joints characterized by focal areas of loss of hyaline articular cartilage, associated with increased activity in marginal and subchondral bone'. These features, when severe, result in the characteristic radiographic changes of reduced interbone distance (joint space narrowing), osteophyte formation, and subchondral sclerosis and cysts. A proportion of people with these changes develop symptoms, including use-related pain in the affected joints, with stiffness after inactivity.

The sites most frequently affected include knees, hips, certain joints of the hands, and the spinal apophyseal joints. Various clinical subgroups have been proposed, both on the basis of joint site, and on presumed aetiology. Osteoarthritis is often described as 'secondary' if a clear abnormality is associated with it, and 'primary' if there is no obvious association. However, if osteoarthritis is a common pathway, produced by a variety of joint insults, multiple association may be apparent.

Osteoarthritis as a public health problem

Osteoarthritis is a common cause of pain and handicap and has a major economic impact on society. It may also be associated with decreased survival, from drug-related morbidity, immobility, and handicap. There are direct medical costs; for instance those of drugs, physiotherapy, and surgery. In the United States an estimated US $1 billion is spent annually on hip surgery alone. There are also ill-effects on productivity, the cost of people functioning below optimum. Those who look after incapacitated patients at home or in hospital add to the costs. Over 180 000 people in the United States are wheelchair-bound by osteoarthritis. There are legal compensation and pension costs. In Quebec in 1983 lumbar pain compensation alone exceded $150 million.

Epidemiology

PREVALENCE: AGE, SEX, AND PATTERN OF JOINT INVOLVEMENT

Radiographic evidence of osteoarthritis increases with age (Fig. 1). Population-based studies show a low prevalence in all joint sites in young adults. In the commonly affected joints (hands, knees, hips, spine) prevalence rates rise steeply with age so that radiographic changes are almost universal in the elderly. Some joints, such as the ankle, are rarely affected. Radiographic osteoarthritis also depends on race and gender. In Caucasians, osteoarthritis of the hip has a roughly equal sex incidence, contrasting with the 2:1 excess in females of knee and hand osteoarthritis. Some of the less commonly affected sites, such as the elbow, are affected more commonly in males.

Fig. 1 The relationship of age to increasing prevalence of osteoarthritis at different joint groups. Radiographic prevalence of osteoarthritis in (a) the hand and (b) the knee.
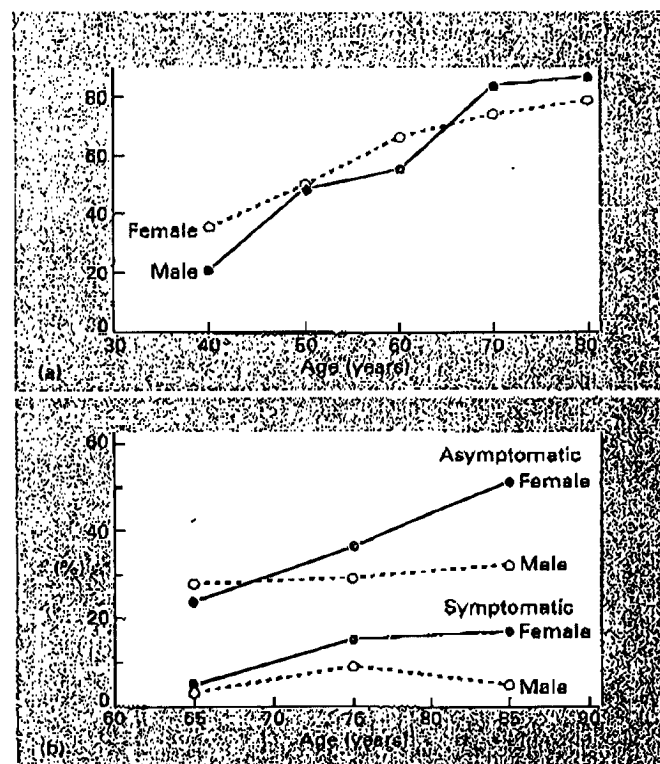
Symptomatic osteoarthritis is less common than radiographic change, many damaged joints remaining asymptomatic. It has been estimated that the overall adult prevalence of symptomatic osteoarthritis is 1 per cent, with some 10 per cent of the over-sixties affected. Common clinical patterns include lone hip osteoarthritis in younger males, knee and hand disease in middle-aged, obese females, and involvement of several joints in the elderly.

RISK FACTORS

If 'wear and tear' were to be the cause of osteoarthritis there should be a close correlation with joint trauma. Untreated fractures through a joint do result in a high frequency of subsequent osteoarthritis, but population studies have failed to show a clear relationship of osteoarthritis to previous trauma.

Studies of occupational groups such as footballers, parachutists, and ballet dancers give confusing results. This may partly be due to other confounding effects, such as hypermobility, which may determine why certain people have certain occupations, but it may also be evidence that the etiology of the condition is multivariate. Development of disease at unusual sites, for example at the ankle in footballers and ballet dancers, and 'miners elbow', suggest repetitive trauma is important. This is supported by studies of mill-workers, showing that the pattern of hand osteoarthritis reflects their repetitive occupation. Knee disease is increased by previous major knee injury and occupations involving frequent bending; and hip osteoarthritis is increased in farmers.

SYSTEMIC FACTORS

Osteoarthritis is now thought to be due to a combination of systemic influences leading to a predisposition to joint damage, and local biochemical influences, which dictate the distribution and severity of the condition (Table 1).

Obesity is an important risk factor for osteoarthritis of the knees, obese women having seven to nine times the risk of contracting tibiofemoral disease, compared to women of average weight. Obesity has

Table 1 *Factors associated with osteoarthritis: severity, symptoms and incidence*

Strong:
Age, sex, familial, geographical, major joint trauma
Weak:
Chondrocalcinosis, occupation, obesity
Uncertain:
Hypermobility, osteoporosis

weak associations with hip and hand disease, and it is unclear how much of its effect is systemic, and how much is biomechanical.

Hypermobility is another predisposing factor that may involve general as well as local factors. In contrast, osteoporosis has a negative association with hip osteoarthritis. Other evidence of systemic predisposition comes from the geographical and genetic data outlined below.

GEOGRAPHY

Osteoarthritis is present in all populations around the world, but there are hints that patterns vary in different populations (Fig. 2). For example, there is a low incidence of hip disease in the Near and Far East, in Chinese and Japanese populations. In contrast, there is a relatively higher incidence of knee disease but low levels of nodal hand disease in Black and sub-Saharan Africans. Sadly there are no population migration studies to help define whether this variation is from environmental rather than genetic factors, although anthropological studies suggest that the pattern of disease has been different in different cultures and at different times.

In addition, endemic forms of osteoarthritis are seen in certain parts of the world:

Kashin–Beck disease

In Manchuria and along the Amur River there is a very high prevalence of a severe disease developing in adolescence with interphalangeal joint, wrist, and metacarpophalangeal stiffness, swelling, and pain. There is

Fig. 2 The geography of osteoarthritis.
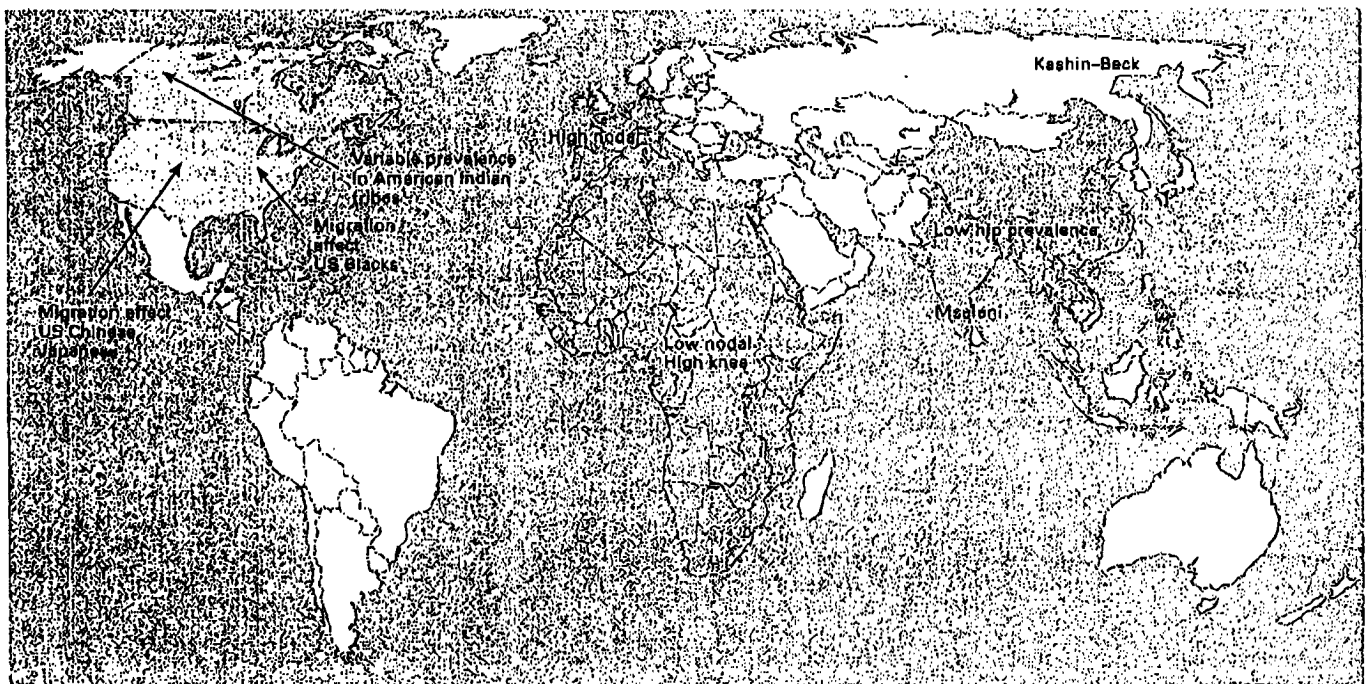
18.6 OSTEOARTHRITIS

irregular epiphyseal growth and premature focal ossification. By early adult life a severe premature osteoarthritis develops with involvement of elbows, knees, and ankles. Hip involvement is uncommon. Histologically there is zonal necrosis of the growth plate. Environmental toxicity by trace metals or mycotoxins has been suggested as a cause.

Mseleni disease

In Natal there is a high prevalence of hip disease with protrusio acetabuli, associated with ankle, knee, shoulder, and elbow involvement; it appears to have a genetic basis.

Genetics

Genetic factors are important in the development of osteoarthritis (Table 2). This is apparent in that 'secondary' osteoarthritis can result from developmental and metabolic disorders like the chondrodysplasias, congenital dislocation of the hip, and ochronosis. Indications of the genetic basis of 'primary' osteoarthritis come from twin studies, family studies, and molecular genetics.

Specific and possible polygenetic effects are shown by a familial tendency, particularly for generalized nodal osteoarthritis, concordance in

Table 2 *Heredity disorders associated with premature osteoarthritis*

Mucopolysaccharidosis type I, aa; II, X; IV, aa
Familial chondrocalcinosis, Aa
Multiple epiphyseal dysplasia, Aa, aa
Spondyloepiphyseal dysplasia tarda, X
Ehlers-Danlos syndrome types I and III, osteo-
   onychodystrophy (nail-patella syndrome), Aa
Progressive hereditary arthro-ophthalmopathy (Sticker's
   syndrome), Aa

identical twins, and the identification of an abnormality in the type II collagen gene in a few families with premature osteoarthritis.

Animal models

Osteoarthritis occurs in most mammals studied, from rodents to chimpanzees. It is rare in the wild, perhaps reflecting a negative effect on survival. It can be induced in experimental animals, by ligament or meniscal removal in the dog, guinea-pig, and rabbit, for example. Some animals such as the SRT/ORT mouse strain have an increased sponta-
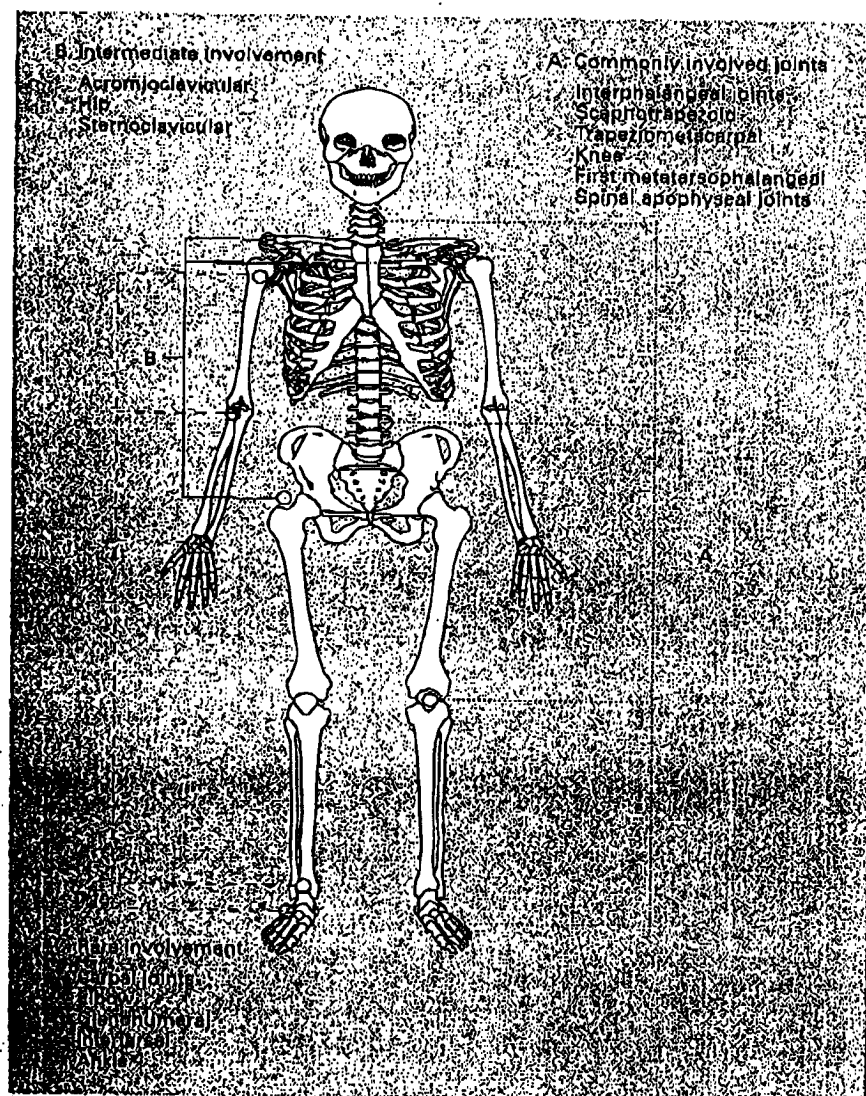

Fig. 3 The pattern of involvement at different joints.

neous incidence of a disease with features of osteoarthritis. These animals have marked variation in susceptibility and experiments have shown that the process can be manipulated by diet, drugs, and sex hormones.

Subgroups

Osteoarthritis is not a single diverse entity. The risk factors outline above vary with joint site (Fig. 3); thus knee disease has strong ass-

Fig. 4 Examples of subgroups of osteoarthritis. (a) The Heberden's node. (b) Scaphotrapezoid, trapeziometacarpal, and metacarpal osteoarthritis in haemochromatosis. (c) Acromegalic hand osteoarthritis. Note joint space widening. (d) Interphalangeal erosive osteoarthritis. (e) Knee osteoarthritis. Anterior and lateral views. (f) Superior pole hip osteoarthritis. (g) Medial pole hip osteoarthritis. (h) Atrophic hip osteoarthritis. (i) Osteoarthritis in congenital dislocation of the hip. (j) Concentric osteoarthritis of the hip with protrusio acetabulae.
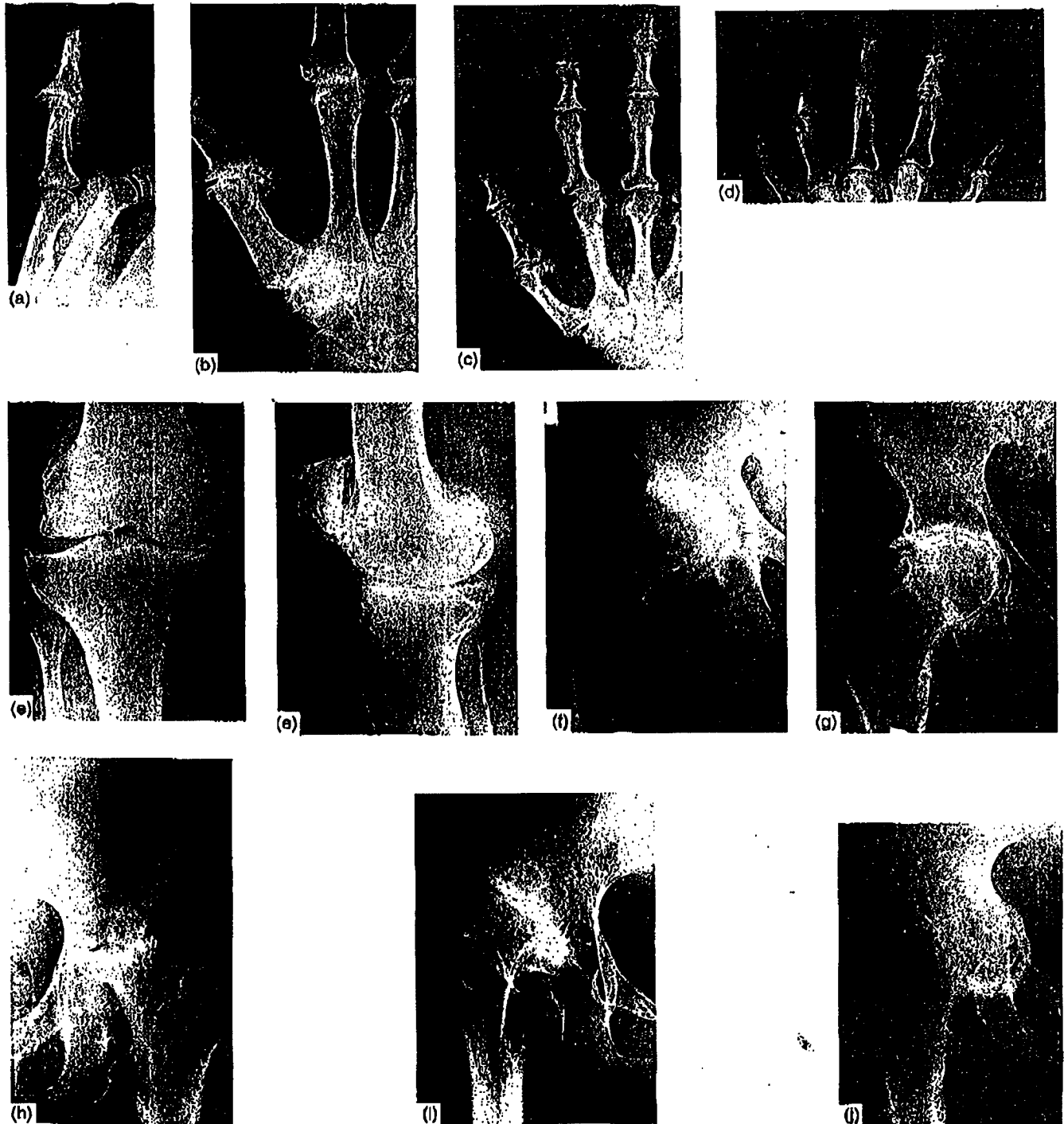
iations with obesity and the female sex, whereas hip osteoarthritis has in equal sex incidence, little or no link to obesity, and a strong association with farming. This indicates that osteoarthritis of each of the major oint sites should be regarded as a different disorder. In addition, the mplication of having developed osteoarthritis in different sites varies—n general, hip and knee osteoarthritis produce much more pain and lisability than does upper limb disease. Subgroups of osteoarthritis can also be distinguished, independent of risk factors and site of joint nvolved:

Examples of subgroups of osteoarthritis are illustrated in Fig. 4.

GENERALIZED OSTEOARTHRITIS

A specific controversy concerns whether or not there is a 'generalized' orm of osteoarthritis. This has been suggested from clinical and epidemiological studies, and it has been defined as involvement of three or more joint groups. If this is a true entity, a common predisposing factor hould result in osteoarthritis developing in all joints; such a pattern hould therefore be a feature of known generalized problems like collagen gene defects. However, there are marked differences in the frequency of individual joint involvement which remains unexplained. The alternative hypothesis is that joints in which it is common for osteoarthritis to develop will be involved, so as to give a generalized pattern surely by chance.

Generalized osteoarthritis is often diagnosed when osteoarthritis involves the distal interphalangeal joints, knees, apophyseal joints of the spine, and first metatarsophalangeal joints. Bony swellings in the distal interphalangeal joints (Heberden's nodes) may form insidiously or from hyaluronate-filled cyst that may be painful and warm. Nodal disease ppears more common in women, with a strong familial pattern. The joint involvement is strikingly asymmetrical, with individual finger joints going through different phases of evolution of the disease; some becoming quiescent and non-painful while others become inflamed and active. This type of nodal hand osteoarthritis is common in women round the menopause and has been termed 'menopausal' osteoarthritis. Polyarticular hand osteoarthritis may be associated with marked inflammation of the joints and the pattern of destruction may include erosive damage. This has led to some cases being classified as 'inflammatory' r 'erosive' osteoarthritis of the hand. Ankylosis of the interphalangeal joints can also occur.

ATROPHIC/HYPERTROPHIC OSTEOARTHRITIS

Classification of osteoarthritis according to the bone response seen on radiographs suggests two polar groups: atrophic and hypertrophic disease—atrophic being rapidly progressive, associated with apatite crystal deposition, and more common with age, while more subchondral sclerosis and osteophytosis (seen in the hypertrophic group) may be associated with a better prognosis.

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (FORESTIER'S DISEASE)

This is a spinal disease characterized by exuberant 'flowing candle wax' ossification bridging at least four vertebral disc spaces, with no loss of vertebral height or disc space. The changes are most marked in the lower thoracic spine. It is associated with calcification of anterior spinal ligament, without sacroiliitis, although there may be para-articular osteophytes. There may be ligamentous calcification around peripheral joints, with whiskering of muscle insertions. It is a common, age-related disorder with an estimated adult prevalence rate of 3.8 per cent in men and 2.6 er cent in women.

Although diffuse idiopathic skeletal hyperostosis is most often symptomatic, backache, stiffness, and pain or tenderness at osseous pars has been described. It is associated with obesity and diabetes. Spinal encroachment can cause myelopathy, and spinal stenosis, and large cervical osteophytes may cause dysphagia. There may be an

Table 3 *Conditions favouring later development of osteoarthritis*

Infection, inflammation
Trauma
Frostbite
With abnormal development
  Congenital dislocation of the hip
  Slipped upper femoral epiphysis
  Perthe's disease
With bone disease
  Paget's disease
  Osteopetrosis
  Avascular necrosis of bone
In metabolic and endocrine disease
  Acromegaly
  Ochronosis
  Haemochromatosis
  Wilson's disease

association between diffuse idiopathic skeletal hyperostosis and the hypertropic type of peripheral joint osteoarthritis, but this remains controversial.

CHARCOT'S JOINTS

A destructive osteoarthritic disease associated with a proliferative bone response is sometimes seen in patients with diabetes mellitus, syringomyelia, meningomyelocele, and neurogenic syphilis. It is non-inflammatory, often with a haemorrhagic effusion. It is probably due to neurovascular, not neurotraumatic, change.

'SECONDARY' OSTEOARTHRITIS

Osteoarthritis may develop following any process damaging a joint (Table 3).

In Paget's disease and osteopetrosis the most common site of osteoarthritis is in the hip. Ochronosis, due to an abnormality of homogentisic acid oxidase results in the deposition of homogentisic acid in connective tissues such as cartilage, and degenerative changes are seen in the spine (with disc calcification), in the knee, shoulder, and hip. Haemochromatosis results in degenerative disease in the metacarpophalangeal, interphalangeal, and shoulder joints, often with pyrophosphate deposition. In Wilson's disease 50 per cent of adults show osteoarthritis changes in metacarpophalangeal joints, wrists, elbows, hips, and knees, and these are associated with periarticular osteopenia.

The localization of osteoarthritis—within and between joints

The commonly affected sites are the spine, hips, knees, hands, and feet. In the spine the atlantoaxial joint, apophyseal joints in the mid-cervical and low lumbar regions, and oncovertebral joints are most vulnerable, probably because these are the sites of greatest stress. Three different radiographic patterns have been identified on the hip joint: concentric, superior pole, and medial pole disease (Fig. 5; see also Fig. 4), stressing the fact that osteoarthritis localizes to specific sites within a joint, as well as to different joint sites. Similarly, at the knee osteoarthritis may affect the medial tibiofemoral or patellofemoral compartments, and in the hand the only sites to be affected commonly are the thumb base (trapezometacarpal and scaphotrapezial joints) and the distal interphalangeal joint. The base of the big toe (first metatarsophalangeal) is the major site involved in the foot.

Pathology

Changes occur throughout an affected joint and can be identified at macroscopic, microscopic, and biochemical levels (Fig. 6).

CARTILAGE

Cartilage becomes fibrillated, thins, and develops 'ulcers' or craters. These changes are usually focal within the joint, becoming more extensive with progression. Areas of new cartilage proliferation may be seen, particularly in association with osteophytes and fibroblast invasion from the marrow. There is invasion by blood vessels into the cartilage across the subchondral plate, and reduplication to the tide mark delineating change in the calcified cartilage layer. Chondrocytes may appear grouped in nests, and other areas have empty lacunae. Fibrocartilage menisci disintegrate.

Fig. 5 Classification of osteoarthritic hip. 1. Normal. 2. Superior pole. 3. Medial pole. 4. Concentric. 5. Dysplastic.
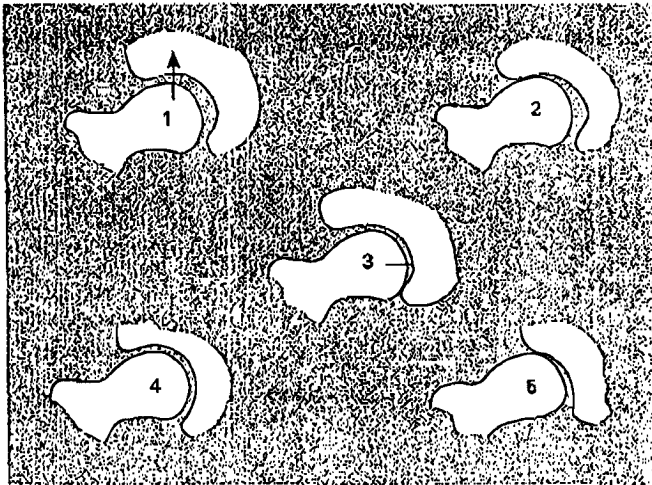

Fig. 6 Pathological features of osteoarthritis.

BONE

The hallmark of osteoarthritis is the change in bone; osteophyte formation, sclerosis, and cyst formation. The subchondral plate and trabecular network thicken. Cortical bone thickens, particularly in the hip to 'buttress' the femoral neck. The cartilage surface may be lost and the exposed bone becomes eburnated—thick and ivory-like. Bony outgrowths, osteophytes develop; there may be formation of subchondral cysts (Fig. 7). The marrow becomes hyperaemic and big sinusoids develop. Late stages of the disease are associated with collapse of the subchondral bone.

SYNOVIUM AND PERIARTICULAR STRUCTURES

The synovium is usually bland. It may contain bone debris, foci of mild, chronic inflammation, and proliferation of fibrous tissue. Tendons hypertrophy and there is wasting of muscle. The synovial fluid may increase in volume and become less viscous. It may contain cartilage and bone debris in addition to crystals, including pyrophosphate and apatite.

Aetiology

MECHANICAL CONSIDERATIONS

Joints are mechanical systems. Understanding how they malfunction and how to modify such malfunction must be considered in this mechanical context. Essentially, joints allow stable, controlled movement of a system of levers under load. The power for movement from muscle is transmitted through tendons to bone. Systems must be designed to

Fig. 7 The formation of bone cysts.
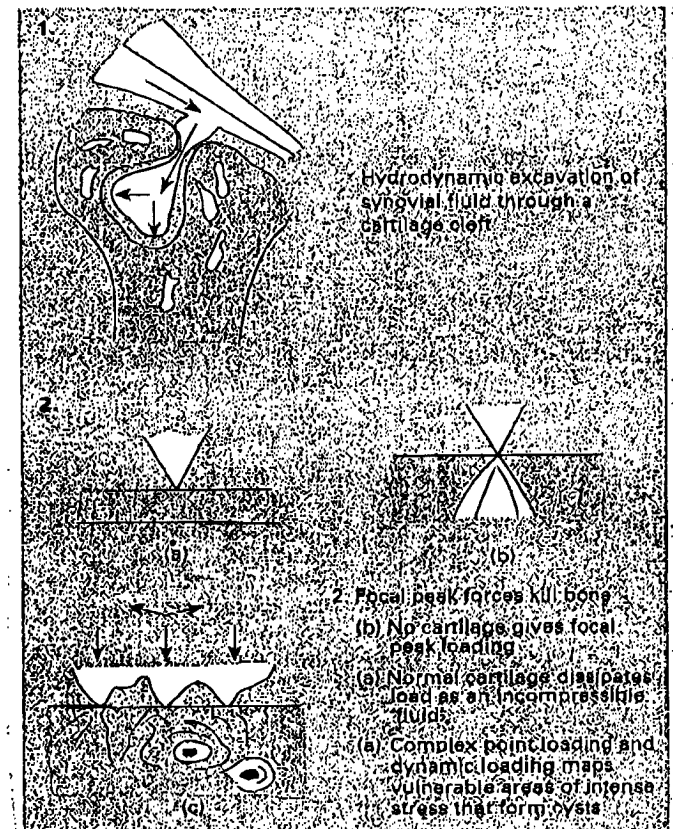
reduce wear of moving surfaces and control fatigue of components during life. Movement with excessive load induces wear. The coeffiecient of friction in the joint surface is below 0.02, but once damage has started this may change. In gel and fluid phases there is also a possibility of cavitation damage. Considerable uncertainty exists whether wear is a problem in normal joints. One possibility is that cartilage continues to grow *pari passu* with wear.

· If loading on a bone increases, the bone will hypertrophy, and the highest loads will produce a fracture: either a fatigue (stress) fracture or a catastrophic disintegration. The transmission of force across non-congruent surfaces results in non-uniform distribution of stress. This distribution will change with movement but results in localized intense foci of force that may prevent viable cell function with resultant development of focal cysts. Cartilage acts like a fluid and disperses load to counteract these forces. However, photoelastic models demonstrate that a change in the character of the cartilage may prevent this dispersion of stress. Cyst formation may result from hydrodynamic stress transmitted through cartilage fissures into bone.

The distribution of cartilage fibrillation in the hip, knee, and elbow in pathological studies shows a focal development in areas of relative disuse: the less loaded areas. For example, the hip areas covered by the acetabulum are less affected than a zone in the periphery and around the fovea. This runs counter to the concept that stressed areas should develop change first, and suggests the reverse: that inadequate loading may be a cause of damage.

· The lack of data on stress distribution *in vivo* underlies the difficulty of identifying whether or not loading keeps the surface intact and inadequate loading induces damage. Immobilized dog cartilage will thin and, if then exercised, vigorously disintegrates with loads that have no effect on joints normally exercised.

The vulnerability of the system to develop these changes and capacity to tolerate damage is a function of the design or any joints. This includes biological factors determining the configuration of the joint and its material composition. Degenerative change will therefore be provoked by factors such as failure of remodelling, design limitation, defects in materials, and control of development.

A unifying hypothesis therefore emerges of osteoarthritis as a common pathway that can be triggered by any damage to a joint, and accelerated by a wide range of factors, although it is difficult to identify independent variables in each case.

Repair

Osteoarthritis may be considered as an ill result or the process of joint repair. The cartilage may not regenerate perfectly as the joint adapts to limit damage and maintain function. The anabolic processes in bone, particularly osteophyte growth, can be seen as part of this response. In progressive osteoarthritis the repair process is inadequate.

Biochemistry

· In experimental osteoarthritis there is an initial increase in cartilage hydration and resultant swelling. There must be a change in the collagen network that restrains the proteoglycan matrix for this to occur. It is unclear how the network of collagen type II is damaged, but changes occur in proteoglycan turnover, altering the size and charge density of cartilage macromolecules, and thus the behaviour of matrix. The increase in chondroitin sulphate is suggestive of the proteoglycan composition of developmental cartilage. Antibodies recognizing epitopes on these 'juvenile' molecules may offer a method of monitoring the progress of osteoarthritis. Proteoglycans may also be important in determining the development of a joint. The limb bud is rich in dermatan sulphate, but with cartilage formation chondroitin sulphate synthesis is turned on. With maturation there is a decrease in chain length. In ageing, at least in bovine cartilage, this is associated with an increase in der-

matan sulphate formation. The collagen subtype profile also changes, with increased synthesis of type II cartilage.

These changes may be mediated by cytokines and hormones. Interleukin-1α and 1β act on the same chondrocyte receptor to increase release of enzymes. α-Tumour necrosis factor acts on a different receptor, to release collagenase and the protoglandin, PGE_2. The chondrocyte also has oestrogen, growth hormone, and somatomedin receptors. For the anabolic response, a switch on of genes controlling cell proliferation and synthesis, changes in the stability of mRNA, or decreased catabolic degradation must occur. Growth factors such as insulin-like growth factor, platelet-derived growth factor, and transforming growth factor β, may be involved in this control.

Clinical features

Osteoarthritis causes pain and joint malfunction. These combine to provide a varying handicap, dependent on a multitude of other factors.

PAIN

Pain must result from changes in the bone or periarticular structures, as hyaline cartilage contains no nerves. Ligamentous strain and inflamed bursae and synovial tissue may also contribute. Pain is characteristically worse on loading, and may be due to secondary effects on loaded tissue such as the bone marrow. In severe disease, night pain is a particular feature, possibly due to raised interosseous pressure.

MALFUNCTION

In joints involved with locomotion, malfunction gives limitation of mobility, instability, stiffness, secondary muscle weakness and pain. Lower limb disease, particularly hip and knee osteoarthritis, cause the greatest problems, resulting in major difficulties with steps, stairs, and walking. Upper limb involvement is uncommon, except around the thumb and interphalangeal joints, resulting in restricted manipulation. In the spine osteoarthritis contributes to postural deformity and causes pain. Osteoarthritis joints are stiff, particularly after resting.

Management

Osteoarthritis cannot be reversed and the aim must be to modify a problem that cannot be eliminated (Fig. 8). The principles of management may be summarized as:

(1) prevention;
(2) early diagnosis and the identification of its causes and complications;
(3) assessment of the main symptoms and dysfunction;
(4) assessment of handicap;
(5) assessment of the patient's emotional, cognitive, and psychological response to the disease.

There is a dearth of guidance from controlled trials, but inference from what is known about osteoarthritis allows a logical plan of treatment to be developed, directed at one or more of these areas.

Prevention is widely practised under different guises; for example, detection of congenital deformity of the hip, reducing trauma, and improving the management of fractures as well as an improved public health policy on exercise, obesity, and fitness; this despite the lack of data on effectiveness of such modifications of lifestyle on osteoarthritis.

Of particular importance in the clinician's approach to the patient is the need to assess the degree of handicap in relation to other problems. For example, if the patient has poor sight, is on inappropriate medication, is under family stress, or is isolated, the osteoarthritis may result in much greater handicap than would otherwise be the case. The psychological response to the disease, possible difficulties in sexual relationships, and the impact on work and leisure activities are important issues, not always properly addressed.

A joint that is unstable and painful may be made less painful and more stable by appropriate aids. In someone who is refusing, or is at too high a risk for surgery, wheelchairs, and adaptations such as bath rails and stair lifts, may make it possible to maintain independence. Walking sticks can be remarkably helpful, but only if used with appropriate attention to detail; for a painful hip or knee, holding the stick in the contralateral hand transfers the weight off the painful joint; for instability, use in the most reassuring hand is appropriate. Splinting to correct instability, correction of varus or valgus at knee and ankle, use of a rocker sole to ease hallux rigidus pain, or a heel raise for leg inequality, all allow reduction of symptoms at low risk. Many people with osteoarthritis find great relief from use of shoes with good shock absorbing insoles, which can reduce pain related to joint loading.

Also important is the correction of the secondary effects of a flexion deformity or muscle wasting. In the knee, quadriceps wasting produces a weak leg with a perception of instability and loss of confidence in movement. Getting up from a chair and using stairs become difficult. If there is a knee flexion, the gait is abnormal and the inequality of leg length tends to weight the painful knee. Exercise, including hydrotherapy, continuous passive motion, and splinting, may correct any deformity, as well as strengthening muscles. Quadriceps exercises have been shown to be an effective way of reducing pain and increasing mobility in people of all ages with osteoarthritis of the knee.

MODIFYING PAIN

In osteoarthritis, drug-related pain control is rarely good, either with simple analgesics, or with non-steroidal anti-inflammatory agents,

Fig. 8 Management of the patient with osteoarthritis.
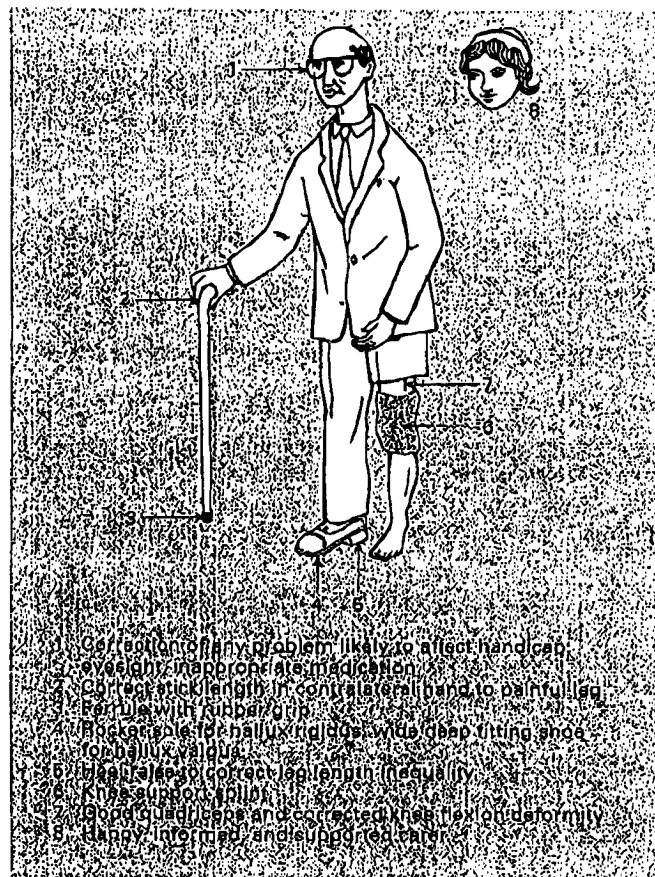
which carry a risk of gastropathy. It is important to appreciate that pa is multifactorial, with exacerbation from mood, fear, uncertainty, ar other associated factors, which may be helped by education and suppor Improved sleep, combined with physical treatment, may reduce the nee for analgesics. Soft-tissue pain may be underdiagnosed, and may follo postural change induced by pain. This and joint pain and swelling ma respond to local steroid injection. Postural pain may alter with chang in the work environment, or advice on posture, sitting, and lifting. Hov ever, uncontrolled pain remains the major indication for surgery.

SURGERY

Arthroplasty has transformed the outlook for people with severe oste arthritis of the hip and knee, but for other joints is still experiment; partly because of the technical problem of surgery and partly from tl lack of understanding of the natural history of the disease in most joi sites.

Other procedures, short of arthroplasty, may be appropriate, partic larly in high-risk patients, to ease symptoms. In the hip, a Girdlestone operation may control pain and allow some mobility. Osteotomy of tl knee, and adductor muscle release at the hip, may allow treatment younger people as well as correcting contributing deformity. Arthrc copy with lavage of debris and meniscal cartilage debridement may ea knee locking and reduce symptoms for a period. Joint fusion will gi a pain-free joint albeit at the cost of immobility.

Investigation

The diagnosis is usually clear from history and examination, continu if necessary by imaging. Analysis of serology and crystallography synovial fluid may be important in excluding other inflammatory di case, and biochemical investigation is occasionally necessary to exclu underlying metabolic causes.

Radiographs remain the major *in vivo* assessment of the bone respon and delineation of osteoarthritis. Their limitation is poor definition soft tissues and lack of information about cartilage unless contrast agen are used. Isotope bone scans show increased activity in osteoarthri joints and can have some prognostic value, but do not contribute diagnosis or management.

Cartilage can be imaged by magnetic resonance, and major advanc in this technique, such as magnetization transfer, are likely to make tl more and more valuable. Methods of following the osteoarthritic proce by tracking biochemical markers of the different processes are also bei developed.

Summary

Osteoarthritis is a poorly understood and complex disease process. Tl complexity and lack of understanding provide a stimulus to the inve tigator, and a challenge to the clinician. It is such a widespread proble that better management must make a substantial impact on the health the ageing population.

REFERENCES

Bland, J.H. and Cooper, S.M. (1984). Osteoarthritis: a review of the c biology involved and evidence for reversibility. Management rationa related to known genesis and pathophysiology. *Seminars in Arthritis a Rheumatism* 14, (2), 106–33.
Bullough, P.G. (1981). The geometry of diarthrodial joints, its physiologi maintenance, and the possible significance of age related changes geometry to load distribution and the development of osteoarthritis. *Cl ical Orthopaedics and Related Research* 156, 61–6.
Danielsson, L.G. (1964). Incidence and prognosis of coxarthrosis Ar *Orthopaedica Scandinavica* S66, 8–114.
Felson, D.T. (1990). The epidemiology of knee osteoarthritis: results fr

the Framlington Osteoarthritis Study. *Seminars in Arthritis and Rheumatism* 20, 42–50.

Hadler, N.M., *et al.* (1978). Hand structure and function in an industrial setting. Influence of three patterns of stereotyped repetative usage. *Arthritis and Rheumatism* 21, (2), 1019–25.

Hull, R. and Pope, P.M. (1989). Osteoarthritis and the collagen genes. *Lancet* ii, 1337–8.

Kellgren, J.H. and Moore, R. (1954). Generalised osteoarthritis and Heberden's nodes. *British Medical Journal* 1, 181–4.

Peyron, J.G. (1979). Epidemiologic and etiologic approach of osteoarthritis. *Seminars in Arthritis and Rheumatism* 8, 288–306.

Radin, E.L. and Burr, D.B. (1984). Hypothesis: joints can heal. *Seminars in Arthritis and Rheumatism* 13, 293–302.

Resnick, D., Shaul, S.R., and Robins, J.M. (1975). Diffuse idiopathic skeletal hyperostosis (DISH) Forestier's disease with extraspinal manifestations. *Radiology* 115, 513–20.

Sokoloff, L. (1968). *The biology of degenerative joint disease.* University of Chicago Press, Chicago.

18.7 Crystal-related arthropathies

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INTRODUCTION

Diversity and terminology

A large number of crystals have been associated with acute synovitis, chronic arthropathy, or periarticular syndromes (Table 1). In practice only monosodium urate monohydrate, calcium pyrophosphate dihydrate, and basic calcium phosphates (mainly hydroxyapatite) are commonly encountered.

The taxonomy of these conditions is not universally agreed. Difficulties arise from our poor understanding of pathogenesis, historical extrapolation from gout to other crystal-related conditions, and multiple terms for the same clinical syndrome. Possible relationships between crystals and disease are outlined in Fig. 1. A 'crystal-deposition disease' is defined as a pathological condition associated with mineral deposits which contribute directly to the pathology. This is probably the situation for all manifestations of gout, for acute syndromes associated with calcium pyrophosphate dihydrate, and for acute apatite periarthritis. The role of non-urate crystals in chronic arthropathy, however, is unclear and confounded by the following observations:

1. Most crystals lack disease specificity and occur in a variety of clinical settings, often unaccompanied by symptoms or other abnormality.
2. Crystal deposition may coexist with other rheumatic disease, most commonly osteoarthritis, and often follows rather than precedes articular damage.
3. Combined deposition of several crystal species is common ('mixed crystal deposition').

For descriptive purposes, confusion may be avoided by itemizing the crystal, the site of involvement, and the clinical syndrome (for example, chronic urate olecranon bursitis, acute pyrophosphate arthritis of the knee).

Crystal deposition and clearance

Many factors determine crystal formation and dissolution (Fig. 2). High solute concentrations alone are often insufficient to initiate crystal formation, and the presence of nucleating factors that aid initial particle formation and the balance of growth-promoting and inhibitory factors are probably more important. Little is known of such tissue factors, although they may in part explain:

(1) the characteristic, limited distribution of different crystals;
(2) the frequency of mixed crystal deposition (via epitaxial nucleation and growth of one crystal on another); and
(3) non-specific predisposition to crystal formation in osteoarthritic tissues (via accompanying alterations in proteoglycan, collagen, and lipid).

Table 1 *Crystalline particles associated with joint disease*

Intrinsic
Monosodium urate monohydrate
Calcium pyrophosphate dihydrate (monoclinic, triclinic)
Calcium phosphates
basic; hydroxyapatite, octacalcium phosphate, tricalcium phosphate
acidic; brushite, monetite
Calcium oxalate
Lipids
cholesterol
lipid liquid crystals
Charcot-Leyden (phospholipase) crystals
Cystine
Xanthine, hypoxanthine
Protein precipitates (e.g. cryoglobulins)
Extrinsic
Synthetic corticosteroids
Plant thorns (semicrystalloid cellulose), especially blackthorn, rose, dried palm fronds
Sea-urchin spines (crystalline calcium carbonate)
Methylmethacrylate

Formation of crystals *in vivo* is a dynamic, although usually slow, process. At any time the crystal load will depend on the rate of formation, the rate of dissolution, and trafficking of crystals away from their site of formation (via 'shedding' from preformed deposits with secondary uptake by synovial and other cells).

Crystal-induced inflammation and tissue damage

Crystals implicated in joint disease are stable, hard particles that exert biological effects via surface-active and mechanical properties. With respect to acute inflammation, they are all markedly phlogistic agents in a wide range of *in vitro* and *in vivo* systems. Surface-active interaction has been demonstrated with:

(1) humoral mediators, for example complement activation via classical and alternative pathways; activation of Hageman factor;
(2) cell-derived mediators, for example superoxide production and release of lysozymes, chemotactic factor, and lipoxygenase-derived products of arachidonic acid by neutrophils; release of interleukin-1, interleukin-6, and tumour necrosis factor by monocytes and synoviocytes;
(3) cell membranes, for example membranolysis of lysosomes,